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The present number is the second of a series concerned with the applications of physics in medicine, the first of which was No 6 of Vol 3. Advantage has been taken of the advice of many of the contributors to this number in evolving its general plan and the range of its subject-matter. In addition, acknowledgment should be made for benefit gained by consultations with Prof W V Mayneord, who contributed the introductory article to the series (*BMB* 721), and Mr L G Grimmett BSc, formerly of the Science Commission, Conference of Allied Ministers of Education, and at present attached to the Preparatory Commission of the United Nations Educational, Scientific and Cultural Organisation.

The history of medicine provides a clear demonstration of the impermanence of therapeutic methods, and the probable future of radiotherapy is a question upon which there can be no unanimity. However, as so often happens in medicine, an originally empirical method of treatment has led to the growth of a new field of scientific study of great intrinsic interest.

DR F G SPEAR is a member of the scientific staff of the Medical Research Council, London, and is well known for his pioneer work in radiobiology. He is deputy director of the Strangeways Research Laboratory, Cambridge, where systematic research in experimental radiology has been done since 1922, when the late Dr Strangeways began his radiological investigations with tissue cultures. Dr Spear is a member of the National Radium Trust and the National Radium Commission. He has published many papers on the biological effects of radiations and in 1930 received the Röntgen Award of the British Institute of Radiology.

DR L H GRAY has been research student in the Cavendish Laboratory under Lord Rutherford (1927-33) and a Fellow of Trinity College, Cambridge (1930-34), when he studied the radiation resulting from the annihilation of positron-electron pairs, and the absolute measurement of gamma-ray energy by ionization methods. In 1933 he was appointed physicist to the Mount Vernon Hospital, and commenced research in relation to the radiotherapy of cancer. His earlier published work was concerned with establishing the fundamentals of the measurement of x - and gamma-ray energy, and particularly in relation to the absorption of energy in living cells. In 1936, in collaboration with Dr J. Read and under the auspices of the British Empire Cancer Campaign, he constructed at the Mount Vernon Hospital the first neutron generator to be built in Britain specifically for biological studies. His numerous papers (many of which were published jointly with other workers) deal with the measurement of neutron energy absorbed in living cells, comparative studies of the effects of gamma rays, x rays, neutrons and other ionizing radiations on enzymes, colloids, chick-embryo fibroblasts, tadpoles, root-tips, and both normal and malignant tissue of mice, and the bearing of these experiments on the use of x rays and neutrons in the treatment of cancer. From 1934 to 1939 he was Proffitt Scholar of the Royal College of Surgeons. Dr Gray is at present senior physicist to the Mount Vernon Hospital, where he is in charge of radiobiological research, and honorary secretary of the British Institute of Radiology. In 1938 he received the Röntgen Award of the Institute.

DR D G CATCHESIDE is lecturer in botany at Cambridge University and a staff Fellow of Trinity College. In the Botany School he is mainly concerned with the teaching of genetics and cytology. His earlier published work dealt with the cytogenetics of the plant *Oenothera*. More recently most of his attention has been devoted to the study of the genetical and cytological effects of x rays and other radiations, especially with a view to discovering the mechanism of this action.

DR D E LEA formerly worked on nuclear physics at the Cavendish Laboratory, Cambridge. In recent years he has been studying various biological actions of radiations at the Strangeways Laboratory, and also in collaboration with a number of Cambridge workers. These researches have been directed at the elucidation of the detailed mechanism of genetical and cytogenetical effects of radiation, of the inactivation of viruses, and the killing of bacteria. Dr Lea has written a book—*Actions of radiations on living cells* (Cambridge University Press, in press)—which summarizes the present state of research in these subjects.

DR A GLUCKSMANN is a member of the staff of the Strangeways

Research Laboratory, Cambridge, where he has been histologist to the radiological section since 1933. He has worked on the histogenesis of normal and malignant tissues, and has studied by quantitative histological methods the effects on a variety of tissues of mechanical stresses, of the action of various chemicals, and of penetrating radiations. In 1942 he received the Röntgen Award of the British Institute of Radiology.

DR G J NEARY is physicist in charge of the clinical work of the physics department at Mount Vernon Hospital and the Radium Institute Northwood, Middlesex. He is a graduate of Cambridge University and worked under Lord Rutherford in the Cavendish Laboratory on the beta-ray type of radioactive disintegration. He joined the staff of Mount Vernon Hospital and The Radium Institute in 1938, where he has given special attention to the practical side of the measurement of x rays and the radiations from radium. He has also made use of mathematical methods in analyzing clinical problems of the distribution of x and gamma radiation and has thereby designed a radically new type of radium applicator for the treatment of carcinoma of the cervix uteri.

DR F ELLIS was medical director of the Sheffield Radium Centre from September, 1930, until May, 1943, when he became director of the department of radiotherapy at the London Hospital. He was the first radiotherapist to install Metropolitan-Vickers' continuously-evacuated x -ray equipment, which he did in 1932. He advocates a considerable measure of standardization of apparatus, and believes that, in treating malignant diseases, the highest dose compatible with complete recovery of the normal tissues is the optimum, and that timing and fractionation should be chosen accordingly. He maintains that dosage should be as uniform as possible throughout the volume treated, and he has applied 'wedge filters' for this purpose and to conserve normal tissue. He has made considerable use of the methods of aspiration biopsy and later "drill" biopsy for obtaining histological material. He believes that the radiotherapist must be primarily a clinician with a physiological and physical imagination. His published work includes papers on tolerance-dosage in radiotherapy with 200 kV x rays, radiotherapy in the treatment of thyrotoxicosis, radiotherapy of malignant disease of the ovary, and the radiosensitivity of malignant melanomata.

DR J READ is physicist to the radiotherapy department of the London Hospital. Earlier he collaborated with Dr L H Gray at the Mount Vernon Hospital in a study of the biological effects of different ionizing radiations, including neutrons and alpha particles, and the measurement of dose of these radiations in comparable units. He is joint author of papers on "Effects of ionizing radiations on the broad bean root," parts I-VI (*Brit J Radiol* 1942-44), "The treatment of cancer by fast neutrons" (*Nature*, 1943, 152, 53), "Measurement of neutron dose in biological experiments" (*Nature*, 1939, 144, 439). Dr Read is a member of the council of the British Institute of Radiology, and of the executive committee of the Hospital Physicists Association.

PROFESSOR S RUSS is physicist to the Middlesex Hospital and professor of physics in the University of London. He has studied many aspects of the reactions of the living cell to x rays and radium, and has participated in the development of modern x -ray and radium therapy. He was for six years scientific secretary of the National Radium Commission.

MR G S INNES is physicist and engineer to the Mozelle Sassoon high-voltage x -ray department at St Bartholomew's Hospital. Prior to this appointment he was engineer in charge of the development and installation of high-voltage continuously-evacuated tubes and rectifiers at Messrs Metropolitan-Vickers Electrical Co., Ltd., Manchester, supervising also initial operations of these equipments in many radiotherapy departments. He has published a number of papers on continuously-evacuated tubes and rectifiers in conjunction with his colleagues and is technical co-author in the recent publication of R. Phillips, *Supervoltage x -ray therapy* (London, 1945).

MR W BINKS is a senior scientific officer at the National Physical Laboratory, Teddington. He is also a member of the National Radium Commission and of the British X -ray and Radium Protection Committee. His published work includes papers dealing with dosimetry and absorption of x rays and radium gamma rays, and with the protection of x -ray and radium workers.

THE BIOLOGICAL EFFECTS OF PENETRATING RADIATIONS

A Review

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Introduction

- 1 Background theory
 - 2 Physical dose and biological response
 - 3 Radio-chemistry
 - 4 Biological indicators
 - 5 Genetical effects of radiations
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Introduction

While Planck was putting forward his theory of energy quanta, Becquerel, by accident, and Curie and Aschkinass, by design, made experiments upon themselves and, with others, demonstrated the destructive action of radium and x rays on living tissues. As a consequence, the biological effects of penetrating radiations became widely studied, in part to satisfy a natural curiosity, but also to determine how the rays might be usefully employed in medicine. The fiftieth anniversary of the discovery (in November 1895) of x rays seems a fitting time to review the trends and some of the achievements in this now vast field of experimental radiobiology, which was born so soon after Röntgen's momentous announcement.

For roughly 25 years biological observations were mainly qualitative and were concerned with the changes seen in a great variety of biological material, after exposure to arbitrarily chosen and crudely measured doses of radiation. By this seemingly haphazard method, however, many facts of fundamental importance were learnt. For example, the selective action of radiation was recognized in the discovery that the cells of some tissues were more affected by a given dose of radiation than the cells of other tissues exposed to the same dose under identical conditions. It was also found that the same dose produced a different result according to whether it was given at a high intensity for a short time or a low intensity for a longer time. It was noted that proliferating tissues showed a more marked reaction to radiation than those without dividing cells and that a latent period, which varied for different types of response, elapsed between exposure and the appearance of radiation-effects.

From about 1920 biological response was, in the laboratory at least, much more frequently measured quantitatively, though all tissues were not equally convenient for experiments of this kind. Some observers chose what was already familiar to them and others what was most conveniently available. Meanwhile, work on the physical measurement of dose made progress culminating in the international unit of measurement for x rays now applicable to gamma radiation as well.

Experimental radiobiology has thus grown to a science

in which physical dose and biological response can be measured with reasonable accuracy. Its development has been greatly influenced by its relation to medicine and, while attempts are sometimes made to distinguish those investigations which have obvious application to medical practice ("applied radiology") from those which have not ("pure research"), opinion would often be divided as to which category any particular investigation should be assigned. At least one major effort has been made to review the literature not immediately concerned with practical radiotherapy (Duggar, 1936). The vast mass of literature which has accumulated on the other side has been the subject of many reviews (Warren, 1928, 1943, Desjardins, 1930, 1931, 1932a, Scott, 1937, Ellinger, 1941, Packard, 1945). The purpose of this paper will, however, best be served by ignoring this somewhat arbitrary division and giving a brief summary of each of the main branches into which the subject has, through circumstance or convenience, become divided.

1 Background Theory

The most conspicuous advances in experimental radiobiology have been made when physicist and biologist have worked in harmonious collaboration, an achievement which in practice is too seldom realized. This is mainly due, perhaps, to a difference in training and outlook which needs to be remedied by re-education on both sides (Mayneord, 1945).

The effects produced by radiations in their passage through living matter may be studied in two ways. The investigation may be concerned with the mechanism of the action of radiation by means of specially designed experiments on selected materials, usually of the simplest kind. This is often referred to as "fundamental research," and is a long-term programme of research in which much detailed information is gradually collected for a particular material, but it does not necessarily follow that what is observed for one tissue applies to other kinds of tissue after similar doses of irradiation. The other, or short-term method, involves a study not of the exact mechanism of the biological action of radiations, but of their histological effects under given physical conditions. Much of this work forms the background of medical radiotherapy, and its results are no less fundamental than those obtained by the other approach, they are sometimes of great practical use.

It was natural, perhaps, that the physicist should be attracted to problems concerned with the mechanism of action of radiation on living cells, while the biologists, in the main, devoted their energies to recording changes in behaviour of irradiated tissues under a variety of experimental conditions. This division of labour has, however, had an unfortunate tendency to sharpen the difference between the physical and biological approach to radiological problems. The result has been the elaboration of theories of action of radiation with, at best, only a limited scope, which have generated a great deal of controversy, not always to the advancement of the science. Theories of action start from the law of Grotthuss and Draper that only absorbed radiation is effective. The physical unit for absorption is the atom. The biological unit is the cell, made up of some 10^{10} molecules in active motion, within which effective radiation energy must be absorbed. Absorption of x rays in matter produces secondary electrons, and it was suggested by Dessauer (1932) that these electronic energies are non-specifically degraded on colliding with protein.

molecules, and that the energy is transformed into the basic process of heat at isolated points

According to Holthusen (Holthusen, 1924, Holthusen & Zweifel, 1932), on the other hand, the energy required for the radiation effects originates from the state of excitation (Bohr) of protein molecules, following the absorption of quanta of radiation, making the molecules capable of new reactions. For example, an increase in intracellular osmotic pressure may result from the formation of substances with smaller molecular weights than the original substance. If the surrounding fluids are not changed to the same extent, this would cause swelling of cells. An increase in cell size after irradiation is known to occur in certain instances (Robertson, 1932, 1935, Lea, Haines & Coulson, 1937, Woodard, 1938), but is by no means common to all cells affected by radiation. A suggestion that radiation caused a re-arrangement of colloid charges (Clark, 1938), which was at first regarded as an alternative mechanism of action, can now be fitted into Holthusen's photochemical theory by regarding the change of charge as a photochemical process.

Ionization rather than excitation became generally regarded as the link between energy absorption and biological response, and a hypothesis which has attracted a great deal of attention was put forward (Crowther, 1926, Curie, 1929, Holweck, 1929, Lacassagne, 1929, Glocker, 1932), according to which there exists in the cell a specially sensitive volume within which ionizations are biologically effective, and these account for the changes subsequently observed. More than one ionization may be required to produce a biological effect, but any ionization which occurs within the cell but outside the sensitive volume is ineffective. This view of the mode of action of radiation has come to be known as the target or "quantum hit" theory, and among its supporters are many physicists. Differences in sensitivity to radiation are explained by the chance distribution of ionizations in the vital volume of the cell. Those who oppose the idea have, perhaps, less well-defined views on radiation action, and are united mainly in their opposition to the theory. As an alternative hypothesis they suggest that a chemical or metabolic change is produced in the cell by irradiation, and they argue that the biological results of physical as well as chemical agents can be explained on the assumption that individual cells differ in their reactions to the changes produced: the weakest succumb first, then the less weak, and the strongest last of all. A great deal of time and effort has been spent in attempts to prove and disprove one or other theory, and most lively controversies have taken place between the contending parties (Scott, 1937). The idea of a compromise has come late, but the results of at least one investigation (Worning, 1937) were shown by the author to be equally well-explained either by the quantum-hit theory or by that of variation in individual sensitivity.

That the target theory holds for particular cases now seems indisputable. It is true in certain instances where the criterion of effect is a lethal action, or a type of injury is produced from which there is no recovery (Lea, Haines & Coulson, 1936, 1937). But it cannot be made to fit all types of biological response to radiation, since by definition it makes no allowance for adaptability in living organisms to changes of environment, including those brought about by radiation. The cell is not inert until it is dead, and so long as it is alive it is capable of a change of behaviour, and with that change

an alteration in its susceptibility to radiation, which cannot be predicted. The types of response must be learned from observation under different biological conditions. For example, the same cell differs in its susceptibility to radiation, among other things, according to its state of dryness, its metabolic activity, its stage of growth, and its age (Petry, 1922, Heilbrunn, 1927, Henshaw, 1932, Scott, 1934, Failla, 1941). There is a danger in attempting too much simplification by physical explanations when dealing with such complex biological material.

2 Physical Dose and Biological Response

The need for a quantitative measure for radiations was apparent as soon as their biological effects had been recognized, and one equally suited to experimental and clinical use was desirable. The question of a biological or a physical basis for radiation dosimetry has been debated for many years. As early as 1918 it was suggested by Russ (1918) that the amount of radiation necessary to kill mouse cancer cells might be used as a standard for which he suggested the name "rad". Since then, many similar methods of dosage have been devised and will be considered under the heading Biological Indicators.

The most practical and useful method of dosimetry, however, is that based upon the ionization produced in air by radiation, originally suggested in 1908, and now developed into the international roentgen (r) of x - and gamma-ray measurement (*British Journal of Radiology*, 1927). Much research has been done to discover under what conditions the ionization in air may be taken as a measure of the dose in living tissues (Mayneord, 1940, Wilson, 1945).

Assuming that ionization in the tissue is responsible for the biological changes produced, the roentgen should be a useful unit for linking physical dose with biological response, since an accurate measure of any well-recognized biological response in terms of the roentgen would enable the experimental conditions to be repeated anywhere by any competent person. The first and most obvious biological response to be recognized was the erythema produced in human skin, and since the tolerance of the skin to radiation is a limiting factor in many radiotherapeutic procedures, the determination of the "skin erythema dose" (SED) in roentgens has been the subject of much careful investigation (Quimby, 1941, 1942). The difficulties of such an apparently simple procedure are, however, considerable. The dose received by the skin is due not only to the incident radiation, but also to scattered radiation which may constitute half the total dose, and which varies with the quality of radiation, the size of the irradiated area, and the particular part of the body (depending on the relative amount of bone, muscle and fluid) being irradiated (Reisner, 1933, Wintz, 1933, Thoraues, 1935, Hudson, 1937, Exner & Packard, 1945). On the biological side, the accuracy of the determination is vitiated, partly owing to individual variation in the response to irradiation, and partly to difference of opinion of various observers as to what constitutes the proper erythema reaction. Taking the results obtained from the majority of observations made, it is possible to compile tables of the approximate value of the SED for different quality radiations falling on a field of given area (Reisner, 1933, Wintz, 1933) or volume of given size (Quimby, 1935). In any one series of observations made under constant conditions by the same observer the doses

are likely to be comparable with each other, but where different series of experiments are considered a comparison of doses must be made with caution

The determination of the SED for different quality radiations has shown a rise in the skin tolerance as the wavelength of the radiation shortens. Large doses of highly penetrating radiations can now be given to a deep-seated tumour with comparative safety to the skin. But with this decrease in absorption of radiation on the skin, there is an increase in the

These considerations illustrate some of the complexities of the irradiation problem where organized body-tissues are concerned. Great technical advances have been made on the physical side in delivering a given dose to a selected volume of tissue, but a stage has been reached when it is easier to deliver a given dose of radiation than to know precisely what biological changes that irradiation produces in the tissue irradiated. It is time now for corresponding advances on the biological side.

TABLE I ILLUSTRATING BIOLOGICAL RESPONSE TO A VARIETY OF RADIATION DOSES

No	Dose in r	Biological Response	Reference
1	10 ⁻⁵	"Safety" limit of exposure for radiographers, etc., per sec	British X Ray and Radium Protection Committee (1943)
2	0.175	Dose received per day by attendants using a 4 gram radium unit	Cade (1940)
3	0.25	"Safety" limit of exposure per day (7-hour day)	British X Ray and Radium Protection Committee (1943)
4	0.5-1.0	Front of fluorescent screen during examination of patient	Lemmel (1938)
5	1.0	Palpating hand of operator using fluorescent screen every 10 min	Lemmel (1938)
6	1.25	"Safety" limit of exposure per day (5 day week)	British X Ray and Radium Protection Committee (1943)
7	8.0	Threshold for mitotic effect in grasshopper	Carlson (1942)
8	9-70	Received by diagnostician making complete radiographic study of gastro intestinal tract (see No. 13)	Jaderholm (1935)
9	15	To either gamete produces developmental abnormalities in 5% of individuals (frog) (see No. 18)	Henshaw (1943)
10	34	Threshold for mitotic effect in chick fibroblasts (cf No. 7)	Spear & Grimmett (1933)
11	40	Alteration in ultra-violet absorption in cell-cytoplasm	Mitchell (verbal communication)
12	50	30% inactivation of enzyme in dilute solution (cf No. 28)	Dale (1943b)
13	50-100	Tube side of fluorescent screen during examination of patient (see No. 8)	Lemmel (1938)
14	170	Temporary sterilization of ovary in women	Wintz (1930)
15	290	Cessation of ovulation	Martius (1931)
16	350	Increases by 1% sex-linked lethal mutation in <i>Drosophila</i> (maximum yield 15% with 5,150 r, above which dose sperm degenerates)	Sturtevant & Beadle (1939)
17	400	Initial injury to ovarian follicles and germinal epithelium of domestic fowl	Essenbun & Karrasch (1940)
18	500	Developmental abnormalities nearly 100% in frog (see No. 9)	Henshaw (1943)
19	800	Follicular disintegration in domestic fowl	Essenbun & Karrasch (1940)
20	1,000	Mean lethal dose for <i>Ascaris</i> eggs	Holthusen (1929)
21	1,039	Average skin erythema dose for gamma rays	Quimby (1941)
22	1,200	Total destruction of male gonads of domestic fowl	Essenbun & Karrasch (1940)
23	2,000	Total destruction of female gonads of domestic fowl	Essenbun & Karrasch (1940) (cf 17, 19, 22 & 23)
24	7,000	Prevents "take" when inoculating benzpyrene induced sarcoma in rat	Halberstaedter, Doljanski & Tenenbaum (1941)
25	9,000-20,000	Inhibits regeneration in worm-segments	Stone (1932), Van Cleave (1934)
26	30,000	Delays cleavage in sea urchin egg	Henshaw (1940)
27	40,000	Causes complete inactivation of frog-sperm	Henshaw (1943)
28	100,000	30% inactivation of enzyme in concentrated solution (x 345 that of No. 12)	Dale (1943b)
29	117,000	Immediate death of chick-fibroblast cultures	Spear (1930)
30	200,000	Mean lethal dose <i>B. mesentericus</i> spores	Lea, Haines & Bretscher (1941)
31	330,000	Mean lethal dose <i>Colpidium colpoda</i>	Crowther (1926, 1938)
32	1,000,000	Inactivation of plant viruses	Lea & Smith (1942)

energy absorbed in the deeper parts of the body, and this, in turn, indirectly affects the "treated area" by the production of adverse constitutional disturbances. This question of body-dose was raised in 1938, when the constitutional effects of telurium therapy were under consideration at the Radium Beam Therapy Research, London (Wood & Grimmett, 1938). It has been systematically developed by Mayneord in a series of publications. For measuring this radiation he suggests a unit to be called the "gramme-rontgen," which may be defined as the energy absorbed in 1 gram of tissue irradiated with one rontgen (Mayneord 1940).

3 Radiochemistry

In studying the effects of radiation on biological material useful information may be obtained from experiments on non-living matter. A recent survey by Allsopp (1944) of the chemical action of radiations has shown how developments in the field of radiochemistry can be related to the study of the biological effects of radiation. Until quite recently, enormous doses of radiation were required to produce measurable chemical changes *in vitro*, and it was suggested that chemical processes could not be involved in therapeutic radiation at any rate, since recognizable changes could be

obtained only with doses far above the maximum human tolerance dose (Scott, 1937)

Recent work by Dale (1942, 1943a, 1943b), however, has shown the fallacy of the conclusion Dale arranged his experimental procedure so that the chemical changes produced by irradiating purified enzymes in aqueous solution were magnified many times by the accompanying changes in biological activity. Dale's results show quite clearly that a constant amount of solute is inactivated for a given amount of radiation-energy absorbed in the whole solution, irrespective of the concentration of the solution. The simplest explanation of these results is that the initial process consists in "activation" of solvent molecules by absorption of radiation, followed by the transfer of energy to the solute by inelastic collision, without the term "activation" being precisely defined (Risse, 1930, Fricke, 1934)

It may be recalled here, however, that in the initiation of radiochemical reactions in gaseous systems, excitation of molecules is apparently more important than ionization, since radiochemical reactions in the gas phase in general follow the same course as the corresponding photochemical reactions (Eyring, Hirschfelder & Taylor, 1936, Hirschfelder & Taylor, 1938, Smith & Essex, 1938). There is no reason to suppose that radiochemical reactions in aqueous solutions are not similarly initiated by energy-carrying solvent molecules (Allsopp, 1944). The experimental evidence is consistent with the hypothesis that the energy-carrier is a free hydroxyl radical (Weiss, 1944)

Since the number of solute-molecules decomposed by a given radiation-dose depends on the concentration of activated solvent produced (not on the concentration of the solute) and will therefore be relatively small, the concentrations of solute employed must be the smallest consistent with chemical analysis, in order that changes in them may be relatively large. It was the widespread failure to recognize this which led to the supposition that significant chemical changes could not be produced *in vitro* by doses within the therapeutic range. For the simplest case, i.e., only one substance in solution, the activation theory would seem a reasonable interpretation of observed facts.

Dale has recently described some striking experiments in which an apparent loss of radiosensitivity occurs when enzymes are irradiated in the presence of various protein and other substrates which share the available energy between them and thus "screen" the original solute (Dale, Meredith & Tweedie, 1943). This work on the protection of one solute by another is a valuable contribution to the interpretation of the chemical effects of radiation *in vivo*. If the indirect-action theory is applicable under these conditions, then a new light may be thrown on the mechanism of action of radiations. From the point of view of a solute, e.g., an enzyme, its inactivation by energy-carriers derived from molecules of aqueous solvent could be regarded as the target theory in reverse. The possibility of this mechanism operating *in vivo*, if only under certain conditions of dilution, is a further caution against making any generalization prematurely.

Whether "activated water" is also connected with such physico-chemical effects as the precipitation of positively charged colloids, viscosity changes, and change of electrokinetic potentials remains to be seen (Crowther, Liebmann & Mills, 1936). It seems more likely that the physico-chemical effects are produced by simple ions (Allsopp, 1944).

4 Biological Indicators

From time to time investigators have sought for a simpler biological material with a more definite and convenient reaction than the skin erythema to serve as a biological dose-unit. When the irradiated tissue is very small, such as the egg of an insect, and is suspended in air so that scattered radiation reaching it is at a minimum, the absorption of energy is uniform throughout the object irradiated and is directly proportional to the intensity of the radiation beam. For example, if a large number of *Drosophila* eggs is exposed to an x-ray beam of unknown intensity for 10 minutes and if, as a result, half the individuals fail to hatch, then 180 rontgen units have been delivered at the rate of 18 r/min (Packard, 1931). The constancy with which such quantitative experiments yield the same result is perhaps one of the most striking features of this type of investigation. With *Drosophila* eggs the error is not more than 3% (Packard, 1936a, 1937), and this order of accuracy is obtained with other types of biological material under laboratory conditions.

A great variety of organisms has now been used as biological indicators of radiation-action by many observers, and each material has its advantages and its limitations. The most important consideration is that the experimenter shall be familiar with the material chosen for experiment, and be able to distinguish with certainty the changes produced by radiation and those unconnected with it.

These indicators are of particular use where the biological effects of two different types of radiation, with no physical unit of measurement in common, are being compared, for example, a comparison of the biological effects of x rays and neutrons (Gray, Mottram, Read & Spear, 1940, Spear, 1944). If the biological response can be matched, then a useful comparison of the physical conditions of irradiation is obtained. Biological indicators are also useful to establish the relationship between injury produced by radiation and other types of injury, e.g., to determine whether the effects of two agents are additive, equal, unrelated, or whether one is capable of potentiating the other (Scott, 1933). The indicators should be small in size, easily available in large numbers at all times, they must show only a small and definite amount of normal variation, and the reaction to radiation must be sharp and easily measured (Holthusen & Braun, 1933). Some investigations may be simplified by using a response which is independent of the time factor. Since radiosensitivity varies enormously with stage of development, it is essential that the greatest care is taken to ensure constancy in age and temperature of the biological indicator selected (Scott, 1937).

Among the materials used in this way, the following may be mentioned, though not all conform to Holthusen's specification for the ideal test-object. Eggs of sea-urchin, *Ascaris*, *Drosophila*, silkworm, grasshopper, frog and axolotl, viruses, bacteria, yeast, pollen grains, protozoa, vegetable root-tips and tissue cultures (Packard, 1927, 1935, Henshaw & Francis, 1938, Packard & Exner, 1945). Germ-cells and somatic cells of higher animals, blood-cells, skin, and even whole animals have also served as indicators in special cases (Eker, 1937).

Such material has been used for demonstrating the wide difference in sensitivity which exists among biological objects. This is illustrated, for the lethal effect, in Table II, taken from data given by Packard (1936b) and by Crowther (1938). The reason for these great differences is quite unknown.

TABLE II DOSE IN RONTGENS NECESSARY TO KILL 50% OF THE SAMPLES OF ORGANISMS IRRADIATED OR TO REDUCE THEIR GROWTH TO HALF THAT OF CONTROLS

Organism	Dose in r
Eggs of <i>Calliphora</i>	40
— — <i>Axolotl</i>	50
— — <i>Drosophila</i>	190
— — <i>Ascaris</i>	1 000
Larva of <i>Drosophila</i>	1 300
<i>Bact coli</i>	5 100
<i>Mesotaenium</i>	9 000
<i>Saccharomyces</i>	42 000
Imago of <i>Drosophila</i>	95 000
<i>B. mesentericus</i>	200 000
<i>Colpidium colpoda</i>	330 000

TABLE III CHANGE IN BIOLOGICAL RESPONSE OF AVIAN FIBROBLASTS GROWN IN VITRO AND EXPOSED TO INCREASING DOSES OF RADIATION

Ray	Intensity in r/m	Duration in hours	Dose in r	Effect
γ	81.5	24	117 000	Immediate death of all cultures
γ	81.5	18	108 000	Death within 2 days of all cultures
γ	81.5	12	58 600	Death within 4 days of all cultures
γ	81.5	9	54 000	Death within 8 days of all cultures
γ	33	24	48 000	Death within 8 days of all cultures
γ	81.5	6	29 000	Death within 10 days of all cultures
γ	81.5	4½	22 000	Death within 13 days of all cultures
γ	81.5	3	14 600	Death within 18 days some cultures recovered
γ	33	9	18 000	Death within 18 days some cultures recovered
x	100	1½	10 000	75% degeneration peak at 3 hours
x	100		5 000	60% degeneration peak at 3 hours
x	100		2 500	50% degeneration, peak at 3 hours
x	100		1 000	7% degeneration at 3 hours count rising
x	100		500	7% degeneration at 3 hours count rising
x	100		100	2% degeneration at 3 hours count rising
γ	33		33	Reduction in mitosis no degeneration ultimate recovery

[The x ray data are taken from Lasnitzki (1943)]

Biological indicators have also been extensively used in studies of the effect of wavelength on biological response, in genetics (see below), and in testing the validity of various theories of action of radiation and the significance of alterations in the physical conditions of irradiation.

The results, though usually consistent for a given material, are often at variance when the response of one material is compared with that of another. Each result has to be considered by itself. The contrast is most marked when the results of irradiating independent biological units, such as bacteria or insect-eggs, are compared with those of an organized colony of cells which make up a body-tissue. This is hardly surprising, since in the one case radiation acts

on single units without any biological spread of effect to adjacent units, and in the other it acts upon cells capable of being further influenced by changes brought about in adjacent cells. However nearly the radiosensitivity of the indicator approaches that of the body-cells (one of Holthusen's stipulations for the ideal test object) it is unlikely to give the *same* information as would be obtained from direct observations on the body-cell. This is the limitation which restricts the usefulness of most of the indicators listed above. Tissue cultures constitute a special case, since the technique enables samples to be taken from the body (before or after radiation), and observations or experiments to be made under the relatively simple conditions of growth *in vitro* for direct comparison with changes seen in similar tissue *in vivo* after similar irradiation treatment (Spear, 1935). An intermediate step is thus provided between the simplicity which is the essence of laboratory experiment, and the complexity of irradiation of organized tissues *in vivo*, which is a very useful guide in comparative investigations.

5 Genetic Effects of Radiation

The demonstration by Muller (1927, 1928) and shortly after by Stadler (1928) that x rays could produce gene-mutations in *Drosophila* and barley excited geneticists throughout the world to take the keenest interest in this property of radiation, x rays immediately became their most important tool for producing mutations. An extensive literature bears witness to the enthusiasm aroused by this discovery, which has opened up a new and large field of research (Cold Spring Harbor Symposia, 1941, Fano & Demerec, 1944, Catcheside, 1945, Lea, 1946). The sterilizing effects of x rays were discovered nearly a generation earlier (Albers-Schonberg, 1903), and much fundamental work on the results of irradiating genetical material was completed before any observations on mutation-production by radiation diverted attention in this direction. These early observations were somewhat restricted, and rarely extended to the offspring of irradiated organisms. The effects of radiation were judged by abnormalities in development after irradiating sperm or ova, or by alterations in the chromosome-configuration of dividing cells. It was later found that radiation may cause an abnormal distribution of hereditary material without change in its composition. Then, as cytological technique advanced, it was realized that the alterations in the chromosomes themselves were of at least two kinds: (i) changes in the linear arrangement of the chromosome threads, resulting from single or double breakage and recombination in new alignments, with or without loss of chromosome fragments, and (ii) changes in the composition of the unit hereditary particles or genes, without disturbance of their position on the chromosome thread (gene-mutation).

Chromosome abnormality offers a very convenient method for making a quantitative measure of radiation effect. The scoring of abnormalities is tedious, but can be made with fair accuracy. Some breaks in the chromosome thread rejoin immediately, but for the rest, the injury, once made, is permanent, so that the result is not complicated by gradual recovery processes. A great variety of structural change is seen after suitable radiation dosage, and this may be classified according to whether one or more chromosome has been involved and how the broken ends have reconnected (Lea & Catcheside, 1942, 1945a). The material is almost ideal for

statistical purposes, because the chromosomes act as targets which mark the hits by breaks in continuity of the thread which can be seen and counted. The tangle in which the broken threads in some cases become involved may cause the breaking up of the cell, or the production of non-viable daughter-cells owing to the unequal distribution of the hereditary material. In this respect chromosome abnormalities are more detrimental than gene-mutations (which may not exert their effects for several generations) since they cause marked infertility in the first-generation offspring.

Structural changes in chromosomes are most easily investigated in insects and plant-cells which have a small number of chromosomes of large size, and they are most easily recognized in the meta- and anaphase of division, at whatever point in the life-cycle of the cell the irradiation is given. The practice of scoring abnormal anaphases as a measure of radiation effect (Marshak, 1937, Marshak & Hudson, 1937) has the limitation, however, that cells irradiated in pre- or early mitotic stages may break down altogether in late prophase or early metaphase. Such cells are therefore missed in the anaphase count.

The total number of breaks produced is proportional to the dose and independent of intensity, but neutrons are more efficient in producing breaks than are x rays (Lea & Catcheside, 1942, Thoday, 1942, Giles, 1943). These observations can be explained on the hypothesis that a chromosome is broken by the passage through it of a single ionizing particle, but that it is necessary for the ionizing particle to be sufficiently densely ionizing for several ionizations to be produced within (or very near) the chromosome. A proton (from neutron irradiation) is sufficient, only the "tail" of a fast electron track gives a sufficient number of ionizations in the given volume. On this hypothesis, x rays of long wavelength should be more effective than those of short wavelength, and this has been found to be the case with an optimum at 4\AA (Catcheside & Lea, 1943). Longer-wavelength x rays produce too short an electron track to span a chromosome, and so their efficiency is diminished.

Changes in the composition of hereditary particles which lead to gene-mutations occur in germ cells of all types, but have been studied most extensively in the case of the fruit-fly, *Drosophila* (Muller, 1930, Lea & Catcheside, 1945a, 1945b, Catcheside & Lea, 1945). A dose of 3,000 r of x rays produces a mutation-rate of about 12%. This is about one hundred times the natural mutation-rate, but qualitatively is indistinguishable from spontaneously-occurring mutations. The yield of radiation-produced mutations is proportional to dose, independent of intensity, and diminishes for equal doses of different radiations in the order x rays, neutrons, alpha rays. It is considered that a mutation in *Drosophila* is the result of a single ionization.

All cells are not equally susceptible to the mutational effects of radiation, and other factors, e.g. temperature, anaesthesia, state of nutrition, and degree of germination, affect the mutation-rate (Hanson & Heys, 1931). Most gene-mutations are recessive, i.e., able to produce their characteristic effect only when paired with another mutated gene of the same kind. Only a minority produce any conspicuous morphological abnormality. Occasionally a change in the gene occurs which initiates new developmental processes (Muller, 1932). A mutation caused by one irradiation may be reversed by a

subsequent exposure (Timofeeff-Ressovsky, 1932). This is exceptional, however, and in nearly every case the mutation-effect is exactly proportional to the amount of energy received, and exactly cumulative over an indefinitely-long period even in successive generations. It is unknown to what extent these observations are applicable to man.

Thus, radiation can be regarded as a useful tool in purely genetic investigations on such problems as the properties of genes and chromosomes, the size and number of genes and their mutational potentialities. Investigations on the genetic effects of radiations provide valuable data on one of the ways in which biological material responds to radiation, but, as rightly emphasized by one of the foremost genetical investigators, "Not all the effects of radiation in killing organisms or disturbing their development are referable to changes either of the class of gene-mutations or chromosome re-arrangements" (Muller, 1939).

6 Injurious and Lethal Effects of Radiation

In previous sections some account has been given of the injuries caused to small organisms (biological indicators) and to particular organs within cells (chromosome effects) by penetrating radiations. There still remains to be considered the largest field of enquiry within the domain of experimental radiology, namely, studies of the effects of radiation upon complex tissues both in health and disease and after experimental injury.

Innumerable observations have been made of the effects of radiation, under the greatest variety of physical conditions, upon embryological development, the various systems of the body at different stages of growth, individual organs and on the body as a whole. Such studies on the response of normal tissues to radiation are not only of interest and importance in themselves, but also because of the information they give concerning the amount of radiation that the healthy body or organ can tolerate. Unless healthy tissue were able to tolerate a greater quantity of radiation energy than diseased tissue, penetrating rays would be of little use in radiotherapy.

In general, biological indicators show a response which is independent of the wavelength of radiation but dependent on the intensity, while the mutation-effect, though dependent on the wavelength, is independent of the intensity. The biological effects now to be considered vary with alteration in both the intensity and the wavelength of the irradiation to which they are exposed.

Radiation affects any given cell of a complex tissue in at least two ways, first by a direct action on the cell, and secondly by injuring neighbouring tissues upon the health functioning of which the cell depends.

The term "indirect effect of radiation" conveniently describes all the effects of radiation except its direct action on the cell, but it has by custom come to be restricted to those effects produced as a result of injury to the blood-supply. This quite arbitrary and rather unfortunate limitation of a useful term requires another to describe the consequences of the action of radiation upon remote tissues and body-fluids. For this the term "constitutional effects of radiation" is now reserved.

When blood-supply is restricted or inhibited by radiation the results are so conspicuous (Harvey, 1942) that it is not surprising, perhaps, that they should at one time have practically monopolized attention. It has even been suggested

that all the radiation effects on a complex tissue are the results of the action on the circulation. This view is easily refuted, however, by reducing the radiation dose below the level which affects the blood-supply, when the direct effects of the radiation can be seen, unmasked by injuries caused from lack of blood. Alternatively, the role of the blood-supply can be demonstrated by irradiating embryos *in ovo* before and after the establishment of the circulation and comparing the results (Wilson, Hughes, Glucksmann & Spear, 1935). So long as the circulation is intact, recovery from the direct effects of exposure is hastened, when the blood-supply is compromised, the injurious results are additive.

The indirect effect of radiation upon embryonic tissue has been strikingly demonstrated by means of tissue-culture experiments (Strangeways & Fell, 1927) in which it was shown that the cells of a 6-day embryo, irradiated *in ovo* and explanted shortly afterwards, could be cultivated *in vitro* in an apparently healthy condition for days. If the embryos were incubated *in ovo* for 21-25 hours after irradiation, however, they showed no trace of growth when explanted *in vitro*. The cause of cell-death was shown to be due to the absence of gaseous exchange in the tissues of the chick when incubated in the shell, resulting from the arrest of the blood-circulation shortly after irradiation.

The level to which the dose must be raised to affect the circulation is considerably above that which causes a direct effect upon tissue cells. For the chick the doses differ by a factor of about 10.

Of the various body-systems, the blood-vessels and blood-forming tissue were among the first in which the direct effects of radiation were observed (Desjardins, 1930, Rolleston, 1930, Dunlap, 1942). These studies have recently been greatly extended by the use of radioactive substances, introduced into the body and selectively absorbed in the blood-forming tissues, in place of external radiation by gamma or x rays. The range of sensitivity of these tissues is remarkable, less than 10 r of x radiation is required to affect the leucocytes of the blood, while a dose of 100,000 r has no demonstrable effect on the isolated (frog's) heart (Scott, 1937, Spear, 1945).

Alteration in the blood-count in man is an early and convenient warning of injurious exposure to radiation, but there is no agreed opinion as to where the danger line can be precisely marked (Russ, 1943). The lymphocytes show the more marked change in patients who have been irradiated, while the polymorphonuclear cells may be the first to show any change in blood-counts of the therapeutic staff. Small doses of gamma rays spread over a long time may lead to a specific aplastic anaemia which is not seen after x radiation.

Exposure to x or gamma rays has pronounced effects on the embryological development of all species of animals which have been investigated. In general, sensitivity during development decreases as the age of an individual increases. This, so far as the direct effect of radiation is concerned, is probably associated with, although not wholly explained by, cell-multiplication and growth-rate. A determination of all the factors involved is one of the central problems of radiation (Hertwig, 1927, Packard, 1931, Henshaw, 1932, Henshaw, Henshaw & Francis, 1933).

Some light is thrown on the problem by studying the inhibitory effect of radiations upon regeneration, which has

demonstrated a differing susceptibility of different types of cells. Or to put it another way—the potencies of specific types of cells play a significant part in determining the result of any given irradiation. There is evidence that, under certain conditions of irradiation, the process of differentiation among embryological cells is promoted (Glucksmann & Tansley, 1936, Tansley, Spear & Glucksmann, 1937), although sensitivity to radiation is lost as differentiation proceeds (Weigand, 1930, Curtis & Schulze, 1934).

The response of the skin and its appendages to radiation has perhaps been more extensively studied than in any other system (Mitchell, 1938, 1940, Martin, 1940, Qumby, 1942). In these investigations the ultimate aim is often to discover ways and means of protecting the skin from injury, while permitting effective irradiation to reach the underlying tissues (Jolles, 1941, Grynkrant & Sitkowski, 1936).

Observations upon the direct effects of irradiation on the generative system of the male rat led to one of the earliest generalizations on the biological effects of radiations (Bergonie & Tribondeau, 1906), which emphasized the relative radiosensitivity of proliferating cells and the relative radioresistance of differentiated cells. Subsequent observations have shown that this applies to all species of animals investigated, though the dose-level at which mitotic activity is affected differs for different species.

While such comparative studies of radiation effects on different biological material have a considerable interest, perhaps more useful information is obtained by comparing the effects of gradually increased doses of radiation on the same type of tissue. This is perhaps most easily seen when the data are arranged in tabular form (see Table III). A definite gradation in the results immediately becomes apparent, especially if the issue is uncomplicated by the intervention of any indirect effects.

The table shows that there is no single type of response which can with any justification be called *the* biological effect of radiation, but that at various dose levels a change in behaviour occurs in the irradiated cells. At the highest dose-level the result is "immediate" death, presumably caused by a breakdown of the physico-chemical structure of cell-protoplasm, at lower dose-levels, however, death of cells results from different kinds of initial injury, at the threshold-dose for any observable change, complete recovery of the cell from the effect of radiation occurs. These dose-levels are altered if the physical conditions of irradiation are changed. Thus, there is a minimum amount of radiation energy required to produce any given type of biological response in organic tissue, which can only be determined by the method of trial and error.

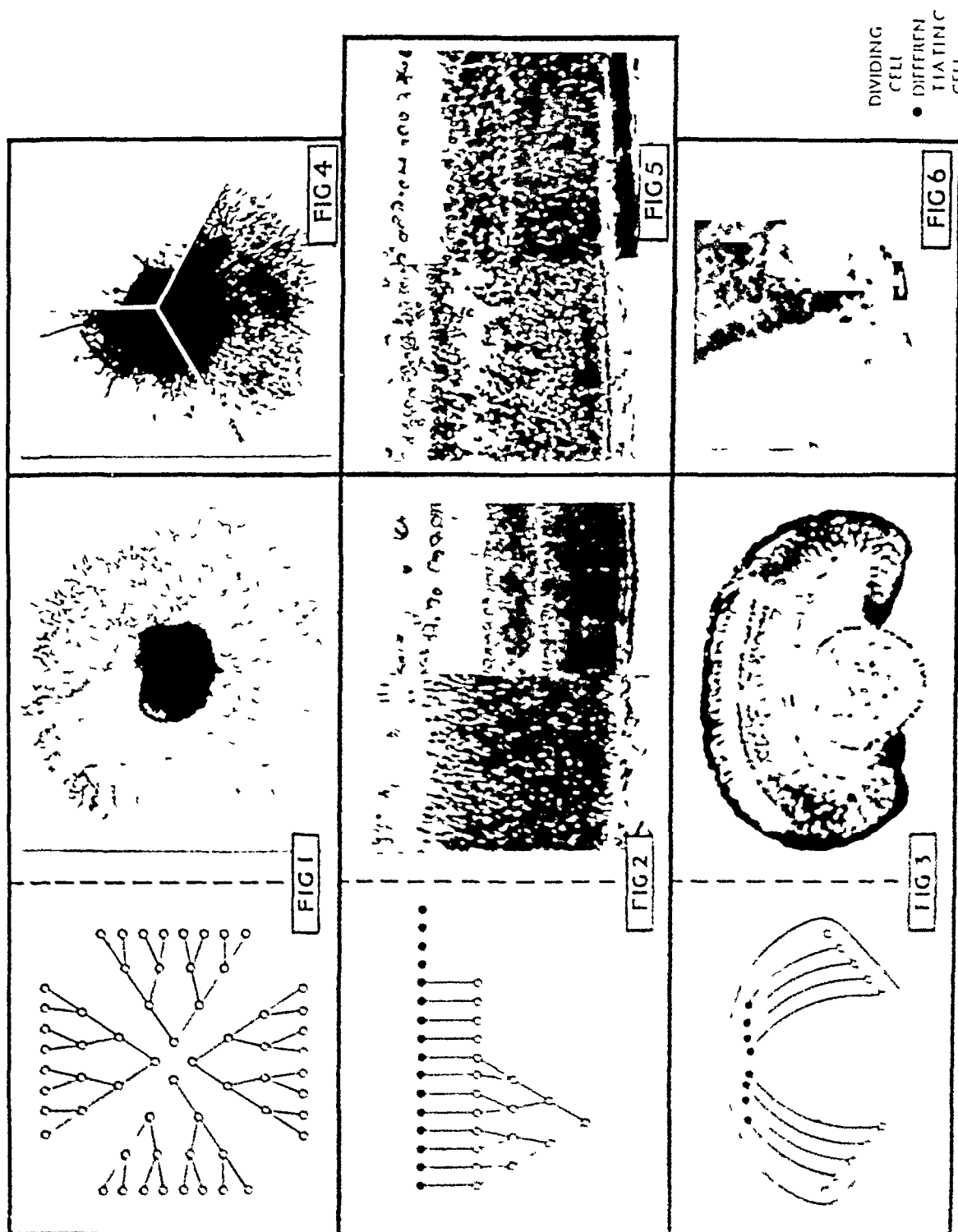
7 Summary of Effects on Normal Tissue

The biological effects of radiation upon normal tissue may be summed up as follows.

Radiations are always injurious to the cells which absorb them, the changes produced may be transitory (reversible effects) or permanent (irreversible effects), with an intermediate class of effect where the radiation-changes disappear completely but leave the tissue in a state of lowered resistance to further radiation (conditioned reversible effect). There is a latent period between irradiation and the recognition of the biological effect it produces (Ellinger, 1941).

There is a ten thousandfold difference between the extremes

PLATE I SCHEME (AFTER GLUCKSMANN) ILLUSTRATING THE RELATIONSHIP BETWEEN CELL DIVISION AND CELL DIFFERENTIATION IN DIFFERENT TYPES OF NORMAL TISSUE—F C 57-5



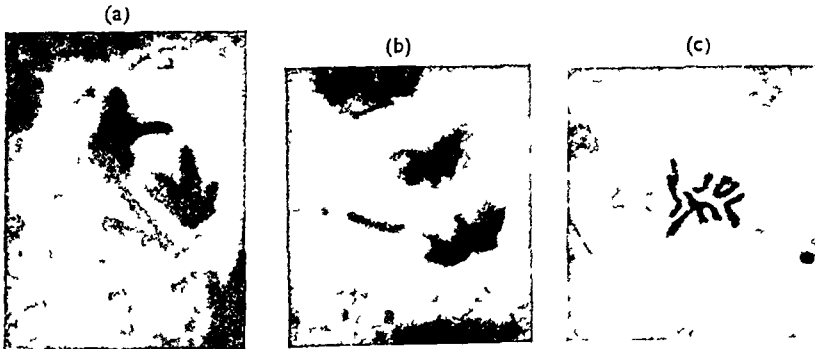


FIG 3

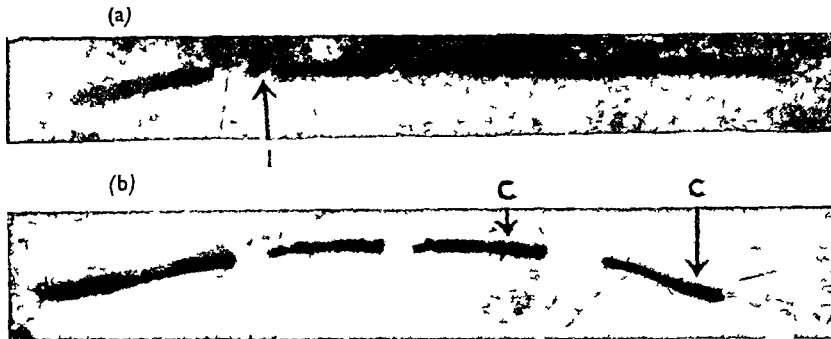


FIG 4

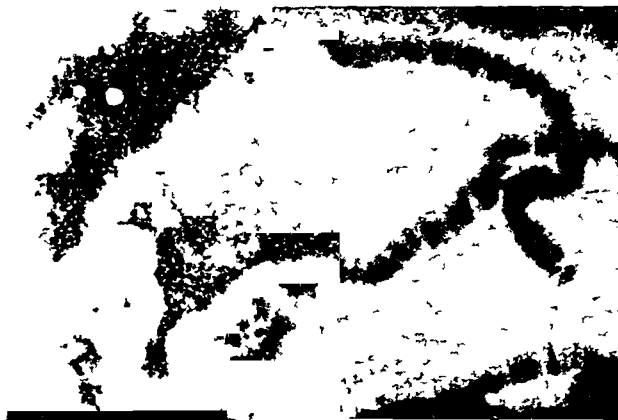


FIG 5

Fig 3 Photomicrographs of chromosomes in *Tradescantia* pollen grains that have been x rayed (a) A dicentric chromosome arisen by sister chromatid-union in a chromosome break, forms a bridge at anaphase joining the two polar groups of chromosomes (b) An acentric fragment-chromosome lags at the equator of the spindle at anaphase (c) Asymmetrical chromatid interchange and a chromosome-break at metaphase

Fig 4 Photomicrographs of chromosomes at metaphase blocked by colchicine in pollen tubes of *Tradescantia* (a) Chromosome break (i) with sister chromatid unions in both the centric and acentric fragments (b) Chromatid breaks, C

Fig 5 Photomicrograph of part of the nucleus of a salivary-gland cell of *Drosophila*, showing an inversion-loop (lower left) The loop is produced by the intimate pairing of the parts of the inversion chromosome with the homologous parts of the normal chromosome

of sensitivity among different types of living cells when measured by the lethal effect (Scott, 1937)

Radiation has a marked effect in interfering with cell-proliferation, and the dose which produces the first recognizable changes in cell-proliferation is always small relative to the direct lethal dose for the same tissue

During development, radiosensitivity decreases as the age of the individual increases, but the decrease is not necessarily progressive throughout development. Sensitivity to radiation is lost as differentiation proceeds, in certain circumstances radiation may promote the process of differentiation. Apart from a direct lethal effect, cells may be so injured by radiation as to be incapable of successful division, and thus either perish on attempting mitosis or produce non-viable daughter-cells. The degeneration which is linked with interference with mitosis can be distinguished from that resulting from the breakdown of the so-called resting cells (Spear & Glücksmann, 1938)

8 Radiation and Malignancy

Much of the experimental work on the biological effects of radiations has some relation to the radiotherapy of malignant disease. The demonstration that radiation can cure a cancerous tumour raises the question of how this effect is brought about. There is a tendency for the results of experiments in any one of the fields of experimental radiology which we have considered to be applied too exclusively to the cancer problem. For example, the effect of radiation upon a proliferating tissue is so striking that it has been suggested that malignant cells die mainly by degenerative mitosis (Lacassagne & Monod, 1922, Nabias, 1928). Although this has been disputed (Donaldson & Canti, 1923, Cheval & Dustin, 1931), the idea has been revived by recent genetical work which has attributed the death of the cancer cell to the effects of radiations on chromosomes.

There can be no doubt that very many irradiated cells die when mitosis is attempted after irradiation. That this action of radiation is frequently due to direct hits on chromosomes seems also beyond dispute. In the light of Dale's work, however, there is now the further possibility that radiation may act also on dissolved enzymes *via* the solvent-molecules, and where dosage is high enough to affect blood-supply, the destructive effect on malignant cells of damage to the circulation is obviously another important factor. Objections can be raised against accepting any *one* of these explanations as the principal means by which radiotherapy achieves its success. Thus, as regards the mitotic effect, the low percentage of dividing cells present at the time of any one irradiation leaves the majority of cancer cells in a tumour unaccounted for, and a high proportion of mitotic cells in a tumour is not in itself an indication of marked radiosensitivity. A direct lethal action upon all tumour cells seems to be excluded (except where radiation is used as a cautery) in view of the high dosage required to produce such an effect under experimental conditions, while the suggestion that all therapeutic effects are the result of an indirect effect of radiation on the blood-circulation is against clear experimental evidence (Desjardins, 1932b) and has never received any substantial support.

The problem can be approached from another angle. Instead of attributing the destruction of a tumour to a single

radiation-effect, irradiated malignant tissue may be examined to see how many types of action can be recognized, and an attempt can be made to assess the relative importance of each in the eradication of the growth. If serial biopsies are taken from tumours during and after radiation treatment, it is possible to follow histologically the changes in cellular activity in a quantitative manner for each type of cell present (Glücksmann, 1941, Glücksmann & Spear, 1945). Radiosensitivity measured by rapidity of disappearance of the tumour soon after irradiation is by no means synonymous with radiocurability, that is permanence of radiation-effect (Cade, 1940). Thus, while much emphasis is often placed on the marked changes produced in anaplastic tumours by radiation, several observers have pointed out that the differentiating tumours, which seem clinically to respond to radiation more slowly, give on the whole a more satisfactory ultimate response (Dominici, 1909, Alter, 1920, Regaud, 1928, Phillips 1931). These clinical results may be explained in the following way. It is obvious that, if sterilization of all potential dividing tumour-cells could be achieved, their total destruction by radiation would be unnecessary, since the altered cells would gradually disappear in the normal course of events. In a differentiating tumour many of the daughter-cells resulting from cell division become sterile because they differentiate, although abnormally. In this connection, the fact that radiation can promote differentiation as well as injuring proliferating cells is of some significance (Fukase, 1930, Finzi & Freund, 1943, Spear & Glücksmann 1941), since, with suitable types of malignant tumour, radiation may exert a curative action both by mitotic inhibition and by sterilization. In the undifferentiated or anaplastic tumour, on the other hand, even a marked destruction of cells following a heavy dosage may lead to a recrudescence of the tumour from residual cells, incapable of sterilization by differentiation which have survived the radiation.

It must be recognized, however, that a tumour, capable of responding to radiation by an increase of differentiation may be adversely affected by excessive exposures which interfere with, instead of promoting, this process. Over-irradiated normal tissues show an increase in cell division and a decrease in cell differentiation which has sometimes resulted in radiation carcinomata (Haagensen, 1931, Laborde, 1931, Ross, 1932). Such growths can, however, be treated by further radiation if it is so delivered that proliferative tendencies of potential dividing cells are checked and the differentiation processes promoted (Williams, 1938).

The conditions under which the inhibiting action of radiation on cell division are best achieved are beginning to be understood, and it remains to determine the best physical conditions for sterilizing cells by promoting differentiation.

In this connection the combination of radiation with chemotherapy would seem a profitable field for future research, as well as the effect of combining two or more different types of radiation in the treatment of a single tumour. The problem needs to be attacked from many aspects—hormonal, genetical, chemical (including organizer-substances), physical, and nutritional—and upon its solution, in all probability, depends the next substantial advance in the treatment of malignancy.

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COMPARATIVE STUDIES OF THE BIOLOGICAL EFFECTS OF X RAYS, NEUTRONS AND OTHER IONIZING RADIATIONS

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The immense literature dealing with the biological effects of ionizing radiations is dominated by experiments in which the radiation employed has been therapeutic x radiation, that is, radiation from tubes operated at voltages of between 80 and 200 kilovolts. This is not surprising, since the majority of the investigations have been undertaken with the object of obtaining information immediately applicable to therapeutic practice. Of the remainder, the approach has more frequently been that of the biologist seeking to explore the effects of radiation on different organisms and on different aspects of cellular activity, than of the physicist attempting to trace one particular lesion—such as a mutation, the breaking of a chromosome, or the inhibition of mitosis—to the interaction of the radiation with a particular set of atoms within the cell.

For the former purpose, the type of radiation employed appeared to be of little consequence, and either the gamma rays from radium or therapeutic x radiation were generally employed as most convenient. For the latter we need to employ a diversity of radiations, so that we may study the effects of changing in a known manner the distribution of the ions produced throughout the cell. Within fairly recent times, comparative studies with different ionizing radiations, such as gamma rays, x rays, neutrons and alpha particles, have led to the establishment of important and often remarkable facts, such as that the death of a cell may result from the generation within a certain small region of an amount of energy which, if spread over the whole cell, would not raise its temperature by more than one hundred millionth of a degree Centigrade. With the advent of the high-voltage x-ray tube¹, the betatron and the cyclotron, the study of the

influence of radiation-type or -quality upon biological response has assumed a practical importance, for with the help of these machines it is possible to generate almost any type of ionizing radiation under conditions which are suitable for the treatment of a deep-seated tumour.

Linear Ion Density, the Distinguishing Feature of an Ionizing Radiation, from the Biological Standpoint

The discovery of radium followed quickly upon the discovery of x rays, and some of the earliest biological experiments with ionizing radiations were carried out with "naked" and "screened" radium. As the screens used were of just sufficient thickness to absorb all the beta rays, the experiments were, in effect, comparative studies of the effects of the beta and alpha rays as they are generated by a small quantity of radium. Striking differences were at once noticed². Hardy (1903) observed that an alkaline solution of serum globulin (i.e. on the negative side of the isoelectric point) was coagulated, and that an acid solution became clearer when exposed to naked radium. When screens were introduced to absorb all the alpha rays, so that the drop of solution was exposed only to the beta rays, no effect was observed even after twenty times the exposure. Chambers & Russ (1912) observed that erythrocytes were haemolysed when exposed to both alpha and beta rays, but not when the alpha rays were eliminated. Colwell & Russ found that, when emulsions of bacteria were exposed to both alpha and beta rays, marked agglutination occurred before the lethal point was reached. When the alpha rays were eliminated, there was no agglutination, although a lethal condition was reached.

A consideration of the physical differences which obtained in these experiments will serve to illustrate important points in the intercomparison of ionizing radiations in general. The beta rays are electrons, that is, particles having $\frac{1}{1836}$ of the mass of a hydrogen atom and carrying unit negative charge, while the alpha particles are helium nuclei having 4 times the mass of the hydrogen atom and carrying two positive charges. Since it was the negatively-charged globulin molecules which were discharged in Hardy's experiments, the effect was at first attributed to the neutralizing action of the positive charge caused by the alpha particles.

¹ [See paper on Million volt therapy (BMB 807) by G S Innes in this number—Ed.]

² A description of these early experiments is given by Colwell & Russ (1922) the literature to 1936 dealing with the biological effects of alpha particles was reviewed by Zirkle (1936).

This now appears in the highest degree improbable³ All the chemical and biological effects so far studied are referable to the excitation and ionization of the molecules in the path of the ionizing particle, and it would be impossible to say of any individual excited or ionized molecule whether it had been produced by an electron or an alpha particle

The essential difference between the two rays lies in the number and distribution in space of the ions and excited molecules which they produce In the second place, it is important to notice that while the beta and alpha particles emitted by naked radium are comparable in numbers, the beta rays have initially an average energy of about a million volts, which is gradually transformed into ionization and excitation throughout a total path of several millimetres of water or tissue, whereas the 6 million volts initial energy of an alpha particle is dissipated in less than 1/20 mm Within the 1/20 mm immediately surrounding the radium, the total number of ions formed by the alpha rays may therefore be several hundred times as great as that produced by the beta rays, and it is not surprising on this ground alone that the alpha rays appeared very much more effective

We shall discuss in detail only experiments in which the total number of ions formed by the radiation per unit volume of tissue has been estimated with reasonable accuracy⁴ From such experiments we learn that biological effect is not in general uniquely determined by the total number of ions, but that it is also conditioned by the spatial distribution of these ions, the effect of a small number of particles, each producing a large number of ions, is not necessarily the same as that of a large number of particles, each producing few ions

To take a concrete example, consider the effect of equal doses (25 rontgen) of beta radiation and alpha radiation on the meristematic cells in the root-tip of the broad bean, *Vicia faba* The total ionization produced in a nucleus 10 μ in diameter is in each case 23,400 ions In the former, the total is made up of the contribution from 500 beta particles, each producing on an average 7 ions per micron of path In the latter, the whole ionization is produced by the transit of a single alpha particle producing ions at the rate of 3,500 per micron The beta radiation will produce an appreciable diminution in mitotic activity 3 hours after irradiation, but the effect on the subsequent growth of the root will be scarcely detectable The alpha radiation has no detectable immediate effect on mitosis, but six days later the average growth-rate of the roots will be less than a third of its normal value, and a small proportion of the roots will cease to grow altogether

The contrast between the effects of beta and alpha rays is sometimes striking, as in the example just given, because these two radiations lie almost at the opposite extremes of the known radiations in regard to the density of the ionization along the tracks of the particles Even in this case, however, the differences are quantitative and not qualitative A sufficiently large dose of alpha radiation has an immediate effect on mitosis, and a sufficiently large dose of beta radiation will kill the roots Radiations intermediate between beta rays

and alpha rays are not always intermediate in the effectiveness of a given amount of ionization, since there may be an optimum linear ion density for any given biological effect which is not at either extreme, but in the cases so far studied

ION DENSITY PRODUCED BY DIFFERENT IONIZING PARTICLES

RADIATION	MODE OF GENERATION	MEAN LINEAR ION DENSITY ions per micron of tissue	IONIZING PARTICLE
Theoretical minimum ion density for any particle - 6.3			
Very high energy beta and gamma radiation	20-30 million volt betatron	8.5	Electron
Gamma radiation	Natural and artificial radioelements	8.5	
	Radium screened by at least 0.5 mm platinum as used in radiotherapy	11	
X radiation	Supervoltage 1000 kV installation	15	
	Deep Therapy 200 kV installation	80	
	X-ray tubes operated at 30-180 kV	100	
	Characteristic X rays	145	
	Cyclotrons operating at 12 million volts	290	
Neutron radiation	Copper K (8 kV)	300	Proton
	Silver L (3 kV)	380	
	8 million volts	460	
	Aluminium K (1.5 kV)	840	
	High-voltage ion tubes	1100	
Alpha radiation	900 kV Deuterium ions bombarding lithium	3700	Alpha particle
	400 kV Deuterium ions bombarding deuterium	4500	
	Natural disintegration of radon	3700	
	Natural disintegration of polonium	4500	
Atomic rays	Artificial disintegration of boron or lithium by slow neutrons	9000	Atomic particle
	Uranium fissure	130000	

As an ionizing particle slows down it produces⁵ ions at an ever increasing rate until it has been brought nearly to rest The ion density therefore increases along the length of the track of any ionizing particle The figures quoted in the table are average values for all the particles generated by a given type of radiation It will be seen that this average value increases with decreasing voltage for each type of particle Thus very high voltage x rays give rise to the particles of lowest ion density, and high-energy neutron radiation is less densely ionizing than low

it has almost always⁶ been found that there is a smooth and progressive variation of effectiveness with the density of the ionization along the track of the ionizing particle irrespective of whether the particle be an electron, a proton or an alpha particle

The subject, therefore, admits of a great simplification, for in general it is not necessary to contrast the numerous types of radiation, but only to discuss the influence of the "linear ion density" on the total amount of ionization required to bring about a given biological effect Experimentally, also, this involves a simplification, since there are sometimes alternative ways of generating particles of a given ion density, as shown in the above table

Certain points of therapeutic interest emerge from a consideration of the data contained in this table It will be

³ In somewhat analogous experiments with colloidal graphite Gray Read & Liebmann (1941) observed that similar changes in the charged condition of the particles were produced by negatively-charged electrons and positively-charged protons The two radiations differed only in their numerical efficiency

⁴ [The measurement of ionization is discussed by G. J. Neary in another article (BMB 803) in this number—Ed.]

⁵ An exception is noted on p 15

observed that strongly-filtered radium gamma rays, the beta rays from radium, and both the beta rays and the x rays from a betatron operated at voltages up to 30 million volts, are all bracketed at the level of 6-8 ions/micron. Theoretically no charged particle can produce less than 6 ions/micron, moreover, the minimum is a flat one, rising particularly slowly on the high-voltage side, as has been checked experimentally by the study of cosmic-ray particles. While therefore, the betatron offers attractive possibilities from the standpoint of radiological technique there are no *a priori* grounds for expecting a marked difference in biological effectiveness between, say, 30 million volt x rays and heavily-filtered radium gamma rays.

A second point in the table, at which large changes in the conditions of generation result in little or no change in the ion density of the radiation produced, occurs in the range of x rays commonly used in radiotherapy. From the biological standpoint, the quality of an x-ray beam may be specified by stating the average ion density of the secondary electrons to which it gives rise in the irradiated tissue. Some of these electrons (photoelectrons) have the full energy of the x-ray quantum, others (recoil electrons) have only a fraction of this energy. As the kilovoltage of the x-ray tube is increased, the energy of both types of electrons increases, but those having only a small fraction of the quantum energy become relatively more numerous, with the result that the mean energy of all the electrons of both types changes only very slowly. Detailed calculation (Lea, 1946) shows that the average energy, and therefore the average ion density of the secondary electrons, is almost constant for all x-ray-quantum energies between 15 and 90 kV—i.e. roughly for the radiations from x-ray tubes operated at all voltages between 30 and 180 kV. In consequence, it is not to be expected that a change in x-ray quality within this range will be accompanied by any appreciable change in the biological effect of a given total amount of ionization per unit volume of tissue.⁶ The number of experimental investigations dealing with this point is legion, because the range of x-ray qualities in

grounds for doubting the accuracy of the inference from ion-density considerations and it would be possible to point to a number of very careful investigations, outstanding among which are probably those of Packard (1927, 1936b) who studied the percentage-mortality among irradiated *Drosophila* eggs, which show particular biological effects to be independent of x-ray quality over this range to a high degree of accuracy. It appears, indeed, almost in the light of a freakish prank of Nature that she should have tempted so many to investigate a region destined to bear so little fruit.

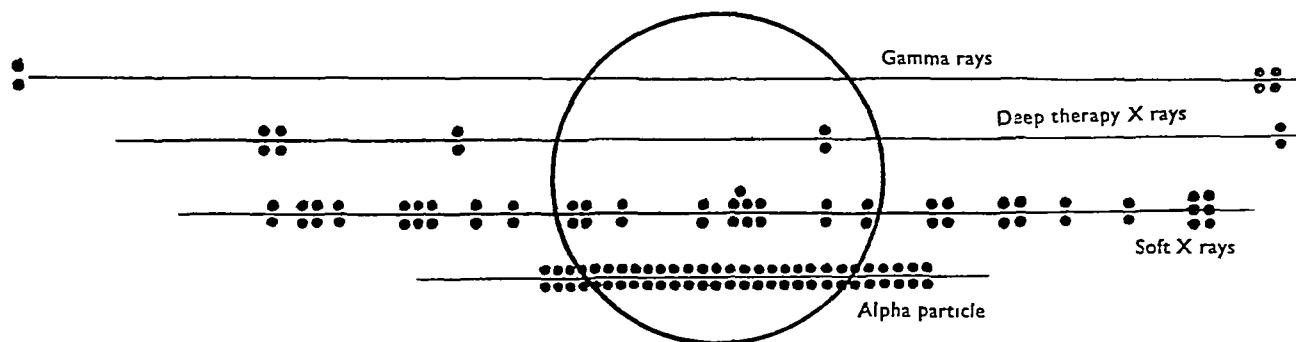
The Influence of Ion Density on Radiochemical Yield

Many substances are decomposed when exposed to any of the ionizing radiations. When the decomposition takes place in the gaseous phase, the number of molecules decomposed is usually of the same order as the number of ions found by the radiation, and is roughly the same for beta rays ($\Delta=10$) and alpha rays ($\Delta=3,500$).⁷ This is true of the decomposition of ammonia, nitrous oxide, and hydrogen iodide. The decomposition of water-vapour, however, appears to be exceptional in that the yield is very low with x rays. Equality of yield with beta and alpha radiation has also been observed in the case of the synthesis of ammonia, hydrogen bromide and ozone, and though there are no published data of this sort for neutrons or other radiations of intermediate ion density, it may be presumed that the yield will be completely independent of ion density in those cases in which it is the same for beta and alpha rays.

Chemical reactions in solution, and particularly in dilute aqueous solution, are of much greater interest from the biological standpoint. The decomposition of water itself is notoriously controversial, even in regard to the experimental facts, and it is not possible to say with certainty whether the much higher yield generally found with alpha radiation than with x rays⁸ is to be referred to differences in ion density or to extraneous circumstances, such as the presence or absence of dissolved oxygen.

The position, as far as the published findings are con-

FIG 1 SEPARATION OF ION CLUSTERS IN RELATION TO THE SIZE OF A VIRUS PARTICLE 27 m μ IN DIAMETER



question happens to be at the same time the most accessible and the most interesting in current radiotherapy. As might be expected, these investigations do not all lead to the same conclusion. It may be said, however, that there are no solid

cerned, is hardly less satisfactory with regard to dilute solutions, since there appears to be no reaction which has

⁶ This does not necessarily imply of course that the biological effect of a given dose, measured in röntgens, will be independent of x ray quality. It is just in this region that the ratio of the ionization produced in tissue to the dose in röntgens may show a marked dependence on x ray quality.

⁷ The symbol Δ will be used throughout for the linear ion density, i.e. the average number of ions formed per micron in water.

⁸ Duane & Scheuer (1913) ($M/N=1.06$). Nurnberger (1934) ($M/N=0.78$). Lanning & Lend (1938) ($M/N=0.87$). M and N refer to the number of molecules decomposed and the number of ions formed respectively.

⁹ Russe (1929) and Fricke & Brownsome (1933) reported a negligible yield but Gunther & Holtzappel (1939) found ($M/N\sim 1$).

been studied at two different ion densities by the same author and the difficulties associated with these experiments are such that small differences in the yield obtained by different authors cannot be relied upon. The evidence in the case of the decomposition of hydrogen bromide and hydrogen iodide, and the reduction of potassium permanganate, points to the absence of any dependence on ion density. It seems fairly clear, on the other hand, that the difference between Stenstrom & Lohmann's estimated yield ($M/N = 0.1$) for the decomposition of tyrosine by x rays and Nurnberger's figure ($M/N = 0.003$) for alpha rays is evidence of a sharp fall in the proportion of molecules decomposed to ions formed by the radiation as the ion density increases from 50 to 3,500 ions/micron. Dale and Meredith, in collaboration with the writer, have recently examined carefully the inactivation of dilute solutions of the enzyme carboxypeptidase by x rays and alpha rays. The alpha-ray yield was found to be only about 1/20 of the x -ray yield, indicating a sharp fall in efficiency of the radiation with increasing ion density. It would appear that, in the case of the densely-ionizing alpha particles, a high proportion of the products resulting from the ionization of the water become ineffective before they reach the enzyme molecules awaiting inactivation. More experiments of this kind are urgently needed to throw light on the mechanism by which such inactivations are brought about in dilute aqueous solutions, particularly in view of their relevance to the biological studies. The influence of ion density on the inactivation of enzyme systems under *in vivo* conditions also awaits investigation.

Ion Density in Relation to the Inactivation of Elementary Biological Units

Perhaps the best-understood examples of ion-density dependence are in connection with the direct inactivation of elementary biological units, such as viruses and genes, by the ionization of their constituent atoms. As separate articles

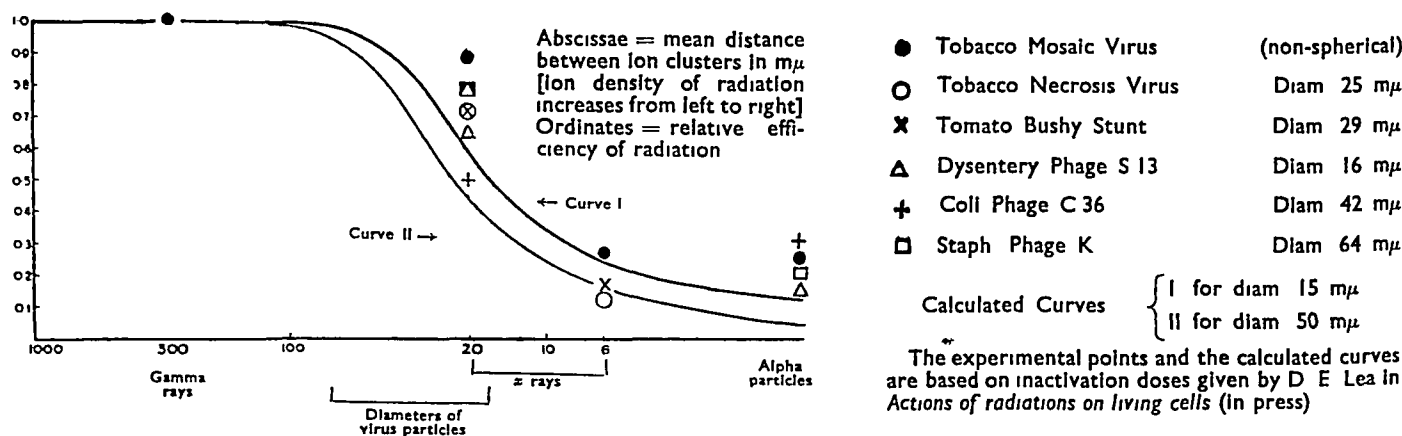
formed in clusters of 1, 2 or more pairs, the average number being 3 pairs, and rather accurate experiments would be necessary to be certain that the effect is invariably produced by a single ion-pair. Whether this is so or not, it is clear that since each cluster contains an average of 3 ion-pairs, the distance apart of the clusters will be given by $3/\Delta$ microns where Δ is the ion density of the radiation. For gamma rays $3/\Delta$ is about 300 $m\mu$, for hard x rays 60 $m\mu$, for soft x rays 20 $m\mu$, and for alpha rays 0.85 $m\mu$.¹²

The diameters of the smaller viruses range from 15–50 $m\mu$. The relation between the size of the virus and the spacing of the ions is thus roughly that shown in Fig. 1 for the four radiations mentioned. Even allowing for unevenness in the spacing of the ion clusters, it is evident that only rarely will a single ionizing particle give rise to more than one ion cluster within a virus particle irradiated by gamma rays. As long as this obtains, the chance that a cluster is formed within any given virus particle is just equal to the total number of clusters formed per unit volume of the medium multiplied by the volume of the virus, and therefore the inactivation-dose should be independent of ion density.

On the other hand, an alpha particle will produce many ion clusters within even the smallest virus particle or gene, so that, if one cluster suffices for inactivation, this radiation must necessarily be inefficient, and a large dose will be needed to produce a given degree of inactivation.

In Fig. 2, the experimentally-determined efficiencies of a number of radiations in inactivating virus preparations are plotted against the mean distance between ion clusters for six virus particles, ranging in size from 16 to 64 $m\mu$. The theoretical variations for spheres of 15 and 50 $m\mu$ diameter are drawn in full. It will be seen that, in accordance with expectation, the experimental values of the efficiency begin to show a dependence on ion density just at the point where the distance between clusters is comparable with the size of the particle.

FIG. 2. RELATIVE EFFICIENCY OF IONIZING RADIATIONS FOR THE INACTIVATION OF VIRUSES



of this series are devoted to viruses¹⁰ and genes,¹¹ a brief reference will suffice.

The distinctive feature of the effects under consideration is that they are produced whenever an ionizing particle leaves two or three ion-pairs anywhere within the unit. It is possible that a single ion-pair suffices, but ion-pairs are, in fact,

¹⁰ [See paper on 'The action of radiations on viruses and bacteria' (BMB 501) by D. E. Lea in this number—Ed.]

¹¹ [See paper on 'Genetic effects of radiations' (BMB 800) by D. G. Catcheside in this number—Ed.]

¹² The millimicron ($m\mu$) = $1/1,000$ micron = 10^{-6} mm

¹³ The term 'efficiency of a radiation' will be used throughout this article to mean a quantity inversely proportional to the total amount of ionization per unit volume of tissue required to produce a given biological effect.

forward the view, before an internal structure was demonstrated by electron micrographs, that vaccinia virus should be regarded as a single-celled organism containing a considerable number of discrete structural units analogous to genes

The Structural Changes Induced in Chromosomes by Different Types of Ionizing Radiation

The nature of the chromosome structural changes induced by radiation is discussed in detail in another article¹⁴ Many of these structural changes are known to be injurious and some to be lethal to the daughter-cells, and they are produced by relatively low doses of radiation—in the materials studied, the doses employed have rarely exceeded 500 rontgens of x radiation, or a tenth of this dose of alpha radiation There can be little doubt therefore that they play an important part in the response of many types of cell to radiation, including probably the response of normal and malignant tissue to x radiation in certain types of radiotherapeutic techniques (Koller, 1945)

Before considering the influence of the type of radiation on the response of cells, organisms, and tissues, it will be convenient to summarize the information regarding the chromosome structural changes The production of a chromosome-break requires that a particle shall pass through (or in the immediate vicinity of) the chromosome, leaving an adequate number of ions within the chromosome The exact number of ions required probably varies from one type of cell to another, and may well vary with the stage of development of any one cell Experimentally it is found that high ion density radiations are more effective than low in breaking the pollen grain chromosomes of the plant *Tradescantia* at prophase (Fig 3), in fact it appears that only radiation which produces at least 200 ions per micron of track has a high break-producing efficiency Since the diameter of the chromatid thread at prophase is about 0.1μ , it is inferred that a break is only likely to follow when at least 20 ions are formed at one locus within the thread No other material has been analyzed for chromosome structural changes in such detail as *Tradescantia*, but a restricted analysis (Marshak, 1939, 1942, Marshak & Bradley, 1945) of the changes produced by x rays and neutrons in root-tips of the broad-bean, the pea, the tomato, three mouse-tumours—sarcoma 180, a mammary carcinoma, and a lymphosarcoma—and a carcinoma and lymphosarcoma of the rat, showed that for all these materials, more structural changes were produced by neutrons than by an equal dose of x rays, from which we may infer that in all these cases the conditions for break-production are of the same general type as those in *Tradescantia* There is some evidence, on the other hand, that in *Drosophila* sperm, a single ion cluster may suffice

Since the ion density along an electron track exceeds 200 ions/micron only when its energy is less than 3.5 kV, not only is much of the ionization produced by the more energetic electrons generated by, say 200 kV x rays, wasted as regards chromosome-break production in *Tradescantia* and similar materials, but any one particle is unlikely to break two chromosomes separated by a distance greater than the range of a 3.5 kV electron, i.e. greater than 0.4 micron

For this reason, structural changes arising from the interchange of partners between two broken chromosomes almost

always involve the action of two separate electrons It follows that when the dose is delivered in a short time, the number of such configurations produced will increase as the square of the dose Furthermore, as the duration over which the total dose is spread is increased, fewer abnormal configurations will be produced because each individual break may reform the original chromosome, and the chance of this happening in preference to an interchange-formation increases with the interval between the production of the two breaks The same restriction does not apply to the recoil protons generated by neutrons or to alpha particles which maintain the required ion density over distances much greater than the diameter of the whole cell It thus comes about that in *Tradescantia*

a Simple breaks produced at any time in the cell-cycle, and certain structural changes (the so-called "isochromatid breaks"), arising from the breaking of two sister chromatids lying almost in contact at prophase, increase in proportion to dose, and are independent of the duration of exposure for all radiations The number produced by a given dose increases with ion density

b Structural changes involving two chromosomes, other than the isochromatid breaks referred to in *a*, increase in proportion to the square of the dose when the exposure-time is constant, and decrease with increasing duration of exposure for all types of x radiation, they increase in proportion to the dose and are independent of the duration of exposure (except in so far as this affects the state of development of the cells irradiated) for neutrons and alpha particles The more-densely-ionizing radiations produce more structural changes of this type per unit dose than x rays when the dose is small and fewer when it is large

It is interesting to note that we have here an exception to the general rule that from the biological standpoint a radiation may be characterized by its ion density Very soft x rays, on account of the limited range of the secondary electrons, do not exactly parallel neutrons, even when the ionizing particles generated by these two radiations have the same average ion density as was demonstrated experimentally by Catcheside & Lea (1943)

c The ratio of the number of certain types of structural change produced by x rays to the number produced by an equal dose of neutrons varies with the stage of development of the cell at the time of irradiation

Comparative Studies with Other Biological Material

Lethal Effect on *Drosophila* Eggs

Many experiments have been made to determine the proportion of fertilized eggs which hatch after receiving varying doses of radiation The eggs are usually irradiated at about 2 hours after laying, when about 8 mitotic cycles have been completed and the egg contains above a hundred nuclei The careful observation of Packard (1927) showed that a given dose produced the same degree of mortality whatever the quality of the radiation within the x -ray therapeutic range, but this, as we have seen, throws little light on the question of a possible dependence of the efficiency of the radiation on ion density Packard (1927), Henshaw & Francis (1936), and others, extended the investigations to supervoltage x rays and gamma rays It appeared at first that a rather larger dose of radiation was needed to produce a given mortality, but the measurements were carried out at a time when some uncer-

¹⁴ [Genetic effects of radiations by D. G. Catcheside (BMB 800)—Ed]

tainty on the physical side was attached to measurements of gamma-ray dose (Neary, 1946). Packard (1932) extended the measurements in the other direction down to 8 kV x rays, and concludes that between 8 kV and 1,000 kV the mortality is independent of x -ray quality. The corresponding range of ion densities is from 150 ions/ μ to 15 ions/ μ .

The effects of 200 kV x rays and neutrons ($\Delta = 400$ ions/) were compared by Zirkle & Lampe (1938). The mortality-curve, as a function of dose, for neutrons had the same shape as that for x rays, so that the relative effects of the two radiations could be expressed by a single figure which was 0.8 for eggs $1\frac{1}{2}$ hours old, 1.2 for eggs $4\frac{1}{2}$ hours old, and 1.1 for eggs 6 hours old. It is doubtful whether the variation with age is significant, and we conclude that neutrons and x rays are roughly equally efficient, i.e. that the effect is independent of ion density up to 400 ions/ μ .

As was mentioned earlier, there is evidence that, under the conditions prevailing in the sperm, the chromosomes of *Drosophila* may be broken by an ionizing particle which leaves only one or two ion clusters within the chromosome-thread. If the same is true of the chromosomes in the egg, then the fact that the mortality does not depend on ion density over the range investigated would not exclude chromosome structural changes as a possible origin of the lethal effect of the radiation. It would be of great interest to investigate the effect of a further tenfold increase in ion density by the use of alpha radiation.

Lethal and Sub-lethal Effects on Root-tips, particularly of *Vicia faba*

The meristematic cells in the shoot and root-tips of organisms are very sensitive to radiation, and the damage caused by 200 to 1,000 rontgen of x radiation will lead to the death of a variety of roots. In passing from gamma radiation ($\Delta = 11$ ions/ μ) to x radiation ($\Delta = 80$ ions/ μ), the efficiency of the radiation has generally been found to increase by about 50%.

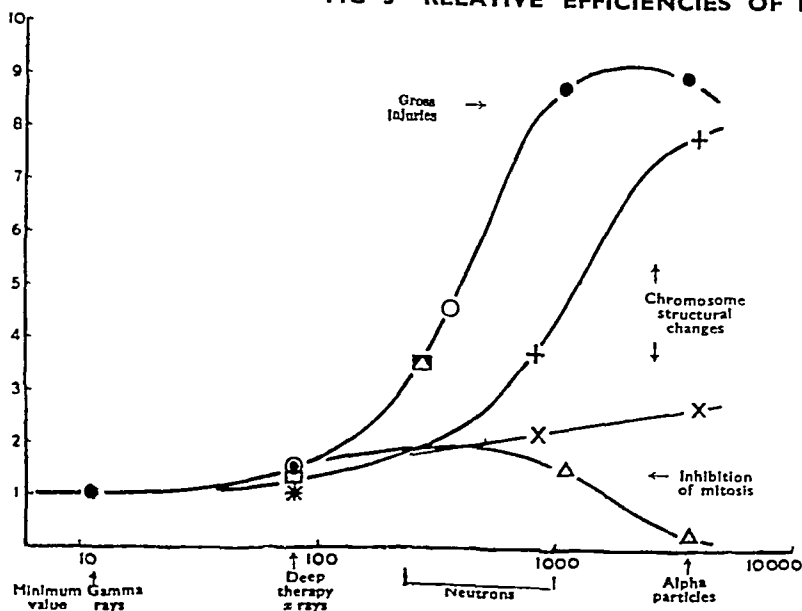
Zirkle & Lampe (1938) compared the inhibition of growth of both the shoot and root of wheat-seedlings, when

irradiated by neutrons, for which $\Delta = 400$ ions/ μ , with that produced by x rays ($\Delta = 80$ ions/ μ). The neutron radiation was about 3 times as efficient as the x radiation, making a total increase in efficiency of 4.5 as the ion density is raised from 11 to 400 ions/ μ . Very similar results were obtained by Gray, Read & Mottram (1939), who investigated the lethal effect of gamma rays, x rays, neutrons, and alpha particles on the roots of *Vicia faba*. Their results are shown in Fig. 3. The wheat-seedling results fall almost on the same curve.

The primary injury is evidently very sensitive to changes in ion density over the range 100–1,000 ions/micron. This is just the region of ion density in which, as we have already seen, there is a rapid increase in the efficiency of ionizing particles in breaking the chromosomes of a variety of materials including *Vicia faba*. Experimental data for two types of chromosome-break observed in *Tradescantia* pollen are also shown in Fig. 3, since corresponding data for *Vicia faba* are not yet available. The trend of one of the curves is similar, suggesting that the inhibition of growth may arise from chromosome structural changes produced in the meristematic cells.

This hypothesis has been tested in a variety of ways, one of which is of special interest from the point of view of ion-density studies (Gray & Scholes, unpublished). It will be recalled that, whereas some types of structural change require the joint action of two ionizing particles when produced by x rays, and therefore increase as the square of the dose and decrease with duration of exposure, all types produced by alpha particles increase in direct proportion to the dose and are independent of duration of exposure. Methods have been evolved of estimating the proportion of cells in the root-tip which are injured by exposure to lethal and sub-lethal doses of radiation, and it has been found that this proportion does, in fact, increase linearly with dose in the case of alpha radiation, and is not diminished by prolonging the exposure-time even up to 24 hours, while with x rays the proportion increases more rapidly than the first power of the dose, and in the case of the larger doses falls markedly as the exposure-time is increased from a few minutes to 4 hours. This inter-relation

FIG. 3 RELATIVE EFFICIENCIES OF IONIZING RADIATIONS



- × Chromatid-breaks } Produced in *Tradescantia*
- + Isochromatid-breaks } pollen-grains by irradiation at prophase
- Inhibition of growth of wheat-seedlings
- Mouse-tumours rendered inviable by irradiation in vitro
- Cessation of growth
- ▲ Temporary inhibition of mitosis } *Vicia faba* roots

Abscissae = linear ion density in ions per μ
Ordinates = relative efficiency of radiation

between the influence of ion density and duration of exposure is likely to be found also when the effects of neutrons and x rays are compared. It is interesting to note (Fig. 3) that the curve for the temporary inhibition of mitosis in *Vicia faba* follows an entirely different course, showing that in this material certain disturbances in the mitotic function must be traced to a different primary injury from that which leads ultimately to the death of the root.

Animal Embryonic Tissue and Tumour-Tissue

The immediate effects of a variety of radiations, from heavily-filtered gamma rays to neutrons, on the mitotic activity of chick-embryo fibroblasts cultured *in vitro* have been the subject of many investigations starting with those of Strangeways, and continued mainly by Spear and his collaborators (Canti & Spear 1927; Gray, Mottram, Read & Spear, 1940; Lasnitzki & Lea 1940). Spear & Grummett (1937) found a marked influence of the hardness of the gamma rays employed which if real would indicate an unusually rapid increase of efficiency with ion density in the region of 10 ions/micron, since the extreme variation of ion density in their experiments could only have been about 30%. The efficiency continues to increase with ion density but more slowly until the x-ray region is reached ($\Delta = 80$ ions/micron) after which there is little if any further increase up to 1,000 ions/micron.

In its general features the course of the curve therefore closely resembles that for the inhibition of mitosis in root-tips, but no data are available to show whether the curve falls at ion densities above 1,000 ions/ μ , as is the case with *Vicia faba* (Fig. 3).

Many experiments by the Strangeways Laboratory team have shown that the effect of radiation on mitosis is essentially the same under *in vivo* as under *in vitro* conditions. In particular, Spear & Tansley (1944) found that, as in the tissue-culture experiments with chick-embryo fibroblasts, the immediate effect of neutrons on the mitotic activity of the developing rat-retina was approximately the same as that of an equal dose of x radiation. There are certain differences in the subsequent return of mitotic activity, but these may be bound up with the markedly greater efficiency of neutrons in causing cell-degeneration.

Not only was much more cell-degeneration produced in the rat-retina by neutrons than by an equal dose of gamma radiation, but the degenerate cells appeared much earlier. This may indicate that cell-degeneration follows a different course according to the radiation which causes the primary injury.

The effects of various radiations have been compared in regard to their ability to injure tumour-tissue by irradiation *in vitro* in such a way that it does not "take" when inoculated into test-animals. It appears to be established, particularly by the careful experiments of Sugura (1939), working with mouse-tumours, that x radiation is about 50% more effective than gamma radiation. The experiments were extended¹⁵ to neutron radiation of ion density about 300 ions/ μ . The relative efficiencies of neutrons and x rays, as tested on a lymphosarcoma, a lymphoma, and a carcinoma of the mouse, were 3, 2.3, and 2.4 respectively. When these data are taken in conjunction with Sugura's, we find that the ion-density curve (Fig. 3) follows closely the course of the curve for the lethal effect on root-tips. Experiments at higher ion density are much needed.

Gray, Mottram & Read (unpublished) carried out *in vivo* irradiations of inoculated mouse-tumours, using neutron and gamma radiation. The neutron radiation appeared to be some 15 times as efficient as gamma radiation. In comparing this result with the *in vitro* studies already mentioned we have to note first that the neutron ion densities were much higher in the *in vivo* experiments ($\Delta = 1,100$ ions/ μ), and, secondly, that the influence of ion density and duration of exposure may be interconnected. The gamma ray and neutron exposures were of equal duration (3 hours), but the time may have been such that the effect of the gamma radiation, but not of the neutron radiation, was thereby diminished compared with a very short exposure.

Mouse tumour tissue has also been irradiated by the very-densely ionizing particles resulting from the disintegration of boron or lithium by slow neutrons. Very great technical difficulties were encountered in obtaining quantitative results in the *in vivo* experiments. An effect of the disintegration-particles was clearly demonstrated in the *in vitro* experiments (Kruger, 1940), though it was not possible to estimate their efficiency relative to other ionizing radiations.

Neutron Therapy

In 1942, Stone & Larkin reported upon 92 patients suffering from malignant disease who had been treated by neutrons. With regard to the clinical results, it is best to quote Stone's (1944) views:

"It is difficult in discussion of effects of a method of treatment tried almost entirely on patients with far advanced cancer to convey any adequate idea of what actually takes place during the course of treatment. While the survival statistics presented and the autopsy findings reported appear discouraging, the general impression of one watching the patients being treated is that marked tumour regressions are being produced even when they were not expected. In many instances, large metastatic nodal involvements disappeared, showing a remarkable effect of the neutron rays on the tumours. The patients as a whole did not react so well, either because the tumour had spread beyond the treated regions and was not controllable for that reason, or because a debilitating ulcer remained at the site of the primary. In many instances biopsies from the edges of persisting ulcers did not show evidence of cancer, but because of either the extensive destruction caused by the cancer or the irreparable damage caused by the neutron rays, normal tissues would not react in such a way as to bring about the healing of the ulcer."

Skin-reactions to neutron radiation followed the same general course as after x radiation. Considerably smaller doses of neutron radiation were needed to produce a given degree of skin reaction, and one may say roughly that the efficiency of neutrons in this respect appears about 2.5 times as great as x rays. It is important to emphasize, however, that, as in x-ray therapy, the total dose was delivered in a large number of fractions spread over about 3 weeks, and until the influence of fractionation on the effects of both types of radiation has been fully investigated, a figure representing their apparent relative effectiveness gives little guide as to the nature of the processes involved (Gray, 1944). It is at least clear, however, that both skin response and tumour response belong to the class of reactions in which, proceeding from gamma rays to neutrons, the effectiveness increases with increasing ion density. It has been pointed out (Gray & Read, 1943) that insofar as more favourable tumour response has been obtained with neutrons than with x rays, this may be taken to indicate that the curve (Fig. 3) for tumour response is rising more rapidly than that for skin-damage. A further improvement might therefore be expected

¹⁵ For a review of this work see Aebersold & Lawrence (1942).

by the use of less energetic (greater ion density) neutrons, and advantage might be taken of the fall in the average energy of a neutron beam on passing into the body to increase the damage to the tumour relative to that to the skin

Such an advantage, however, falls into the same class as the technical improvement offered by the increased depth-dose obtained with high-voltage x-ray tubes¹¹ and betatrons. At best, they enable the therapist to deliver any desired dose of radiation to a mass of tissue which completely envelops all the malignant cells. There remains the problem of dis-

criminating between two adjacent cells in such a manner as to destroy either the malignant character of the tumour-cell or the cell itself, without destroying all its healthy neighbours. Such discriminations must be based ultimately on a biological difference between the two cells. Differences in metabolism, chromosome structure, and rate of development, are known to exist, and these differences, as we have seen, profoundly affect the manner in which the various functions of a cell are influenced by radiations of differing ion density. It would seem that a fuller investigation of these differences may reveal improved methods of obtaining the desired discrimination.

¹¹ [See paper on "Million volt therapy" (BMB 807) by G. S. Innes, in this number.—Ed.]

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GENETIC EFFECTS OF RADIATIONS

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Genetics is concerned with the mechanism of heredity, with the reasons why offspring resemble their parents and in some cases differ from them. The characters of the human body, or of any other organism, are controlled by genes present in every cell. The genes are passed from parent to offspring in the gametes. They are situated in and largely, if not wholly, constitute the chromosomes, of which there is a fixed number in a given kind of organism. The gametes contain a haploid¹ set (n), the zygote and body-cells a diploid set ($2n$) of chromosomes. Thus each chromosome or homologue is represented once in the gamete and twice in a body-cell.

Each gene occupies a fixed position (locus) in its particular chromosome of the haploid set. The gene present at a given locus may not always be exactly the same one, but may be replaced by a slightly different one, called an allelomorph

(or allele). Thus, at a particular genetic locus in two homologous chromosomes, a given body-cell may possess the same allelomorphous gene and be homozygous, or may possess two different allelomorphs and be heterozygous. The number of allelomorphs of a given gene is not limited. Thus 4 allelomorphs controlling the AB blood-group series are recognized in man, about 20 allelomorphs of the w (white eye) series in the fruit-fly *Drosophila melanogaster*, and between 40 and 50 allelomorphs of the gene concerned with incompatibility-reactions of pollen-grains to style in certain self-sterile flowering plants. However, in a normal diploid organism no more than 2 allelomorphs of a gene may be present together in the same individual. Moreover, each of the gametes produced by a given individual will contain only one allelomorph and, where the individual is heterozygous, half its gametes will possess one allelomorph and half the other. For example, the rare nervous disease Huntington's chorea is transmitted, on the average, to half the affected person's children. The particular genes of the affected persons may be symbolized as H for the abnormal gene responsible for the manifestation of the disease and h for its normal allelomorph. The affected person would be Hh and his (or her) gametes half H and half h . Since the disease is so rare, the spouse would normally be hh and the children therefore, on an average, half Hh (capable of developing the disease) and the other half hh (normal).

¹Gr απλός, simple

The gene (*H*) for Huntington's chorea is usually spoken of as being dominant to the normal gene (*h*) which is recessive. In fact, the term dominant implies that there is no difference in the appearance (phenotype) of *HH* and *Hh* individuals. In man this particular information is lacking, so the use of the term "dominant" in this connection is convenient rather than correct. Probably a majority of genes producing abnormalities in man are strictly recessive, the homozygous and heterozygous normals being alike, or else intermediate in their dominance, the heterozygous being more like the homozygous normals than the homozygous abnormal which may be very extreme in their character.

Gene-segregation is orderly and dependent upon the regular pairing together and separation of the chromosomes at meiosis. This precedes gamete-formation and is constituted by two special nuclear divisions, in the course of which the number of chromosomes contributed to the daughter nuclei becomes half that in the parent nucleus. The orderliness is such that each daughter nucleus receives one each of the *n* different homologous chromosomes. Moreover, in any particular gamete a given homologue may be compounded of complementary parts of the two homologues present in the parent. Thus a parent which in one of a pair of homologous chromosomes has the genes *ABcdeFGH* and in the other the genes *abCDEfgh*, may produce gametes which possess for example *ABcdeFGH* or *abCDEfgh* as well as chromosomes like one or other parental homologue. This orderly rearrangement comes about by crossing over during meiosis, the relative frequency of rearrangement occurring between two particular genes being a measure, technically known as the linkage value, of their distance apart on the chromosome. All the genes or loci present in one chromosome together constitute one linkage-group, the number of possible groups in an organism being equal to the haploid number of chromosomes. For a further account of genetics particularly in relation to man the reader is referred to Ford (1942).

Stability of Chromosomes and Genes

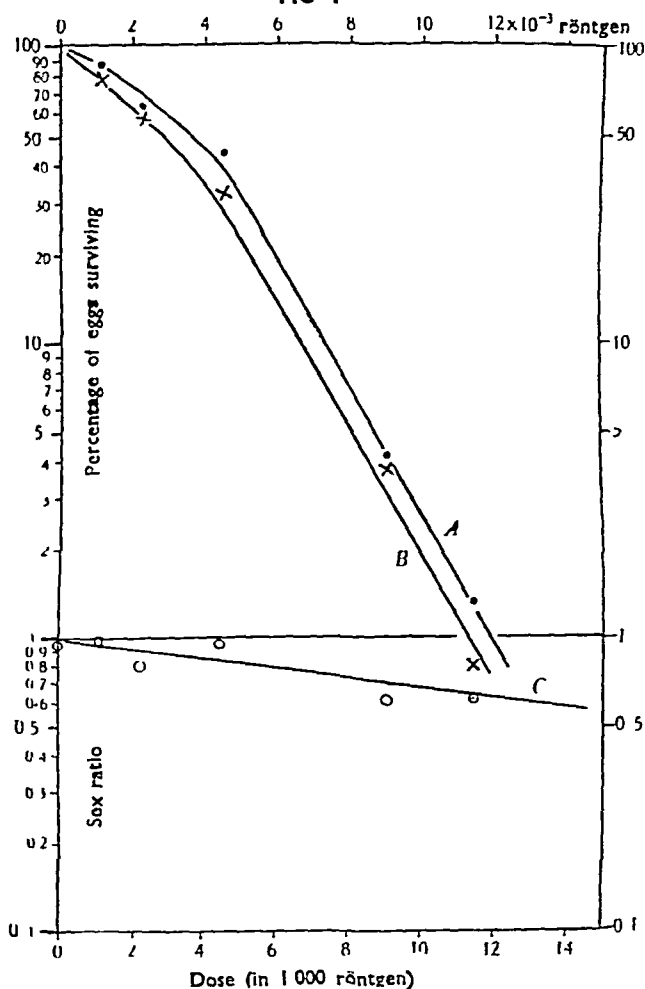
Apart from the process of crossing over, whereby the chromosomes may recombine their differences, the chromosomes are highly stable structures. However, changes do occur very rarely, resulting in alterations in the linear order of the genes within one chromosome or linkage-group, or exchange of blocks of genes between two non-homologous chromosomes or linkage-groups. The frequency of these structural changes, spontaneously very rare, is greatly increased by various radiations. Similarly the genes themselves also possess a high degree of stability. They have a capacity of self-reproduction which is one of the most important characteristics of living matter. All the evidence indicates that they reproduce exactly, and that, if any change occurs within one of them, the gene reproduces in its changed form.

Changes in genes do occur spontaneously, but usually the frequency of such mutations is very small. The normal frequency is of the order of one change per million genes per nuclear division cycle, and may be smaller even than this for a great many genes. A few genes are highly mutable, with a rate of about one per thousand or ten thousand genes per nuclear cycle (Demerec, 1935). There is, however, no indication that they are fundamentally different from the stable genes, and probably there is no discontinuous range in mutation-frequency.

The stability is very little affected by ordinary environmental fluctuations, temperature being the most potent of such influences. A 10°C . rise in temperature will increase the rate of mutation about five times (Timofeeff-Ressovsky, Zimmer & Delbrück, 1935). Thus the principal hereditary material, the chromosomes and genes of which they are constituted, is distinguished by a remarkable stability of minute structure, both as regards the constituent particles, the genes, and the way in which these are ordered and bound together to form chromosomes.

The significant genetic effects of radiations are that gene-mutations and chromosome structural changes become much more frequent under their influence. The order of increase over spontaneous changes is a hundredfold for quite moderate doses of x rays. The chief biological interest lies in the possibilities of studying the nature of the mutation-process and, by extension, of the gene itself, and also of the manner

FIG 1



Relation of frequency of dominant lethals produced in sperm to dose of x rays employed. A = percentage of eggs hatching, B = percentage of eggs producing adult flies. C = sex ratio. In each case the logarithm of the frequency is plotted against dose, points experimental.

Reproduced from Catcheside & Lea (1945) by kind permission of the Editor of the *Journal of Genetics*.

in which the genes are tied together to form chromosomes. With the help of radiations, experiments can be carried out which, if dependent on spontaneous mutation alone, would be almost impossible.

Medically, the importance lies firstly in the fact that most mutations are recessive and deleterious and therefore that deep radiotherapy may run the risk of producing mutations in the gonads. The mutations may be transmitted to the treated person's children and spread undetected in the population in which, generations later, homozygous defective individuals may arise. The genetic change is immediate but the physiological consequences are delayed. Secondly many kinds of induced chromosome structural change are lethal to all cells in which they are produced, and it is this property, among others, of radiations that renders them effective in killing unwanted tissues such as cancers.

Apart from radiations, only a few agents have been found capable of greatly enhancing mutation-rates. The most effective are certain synthetic chemicals, the naturally-occurring mustard oil, allyl isothiocyanate (Auerbach & Robson, 1944) and antibodies (Emerson, 1944).

Most researches on the genetic effects of radiations have been confined to a few organisms that are technically favourable from the point of view of ease in handling the large numbers of individuals needed in controlled experiments. The principal ones are the fly *Drosophila melanogaster*, maize, and some fungi such as *Neurospora*, together with the flowering plant *Tradescantia* for chromosome studies.

Radiation-induced Mutation in *Drosophila*

When adult male flies are exposed to radiations and subsequently mated to untreated virgin females, a proportion of the eggs laid fail to hatch although they have been fertilized. The premature death of the individual is ascribed to the induction of a dominant lethal mutation in the sperm. The existence of such mutations was first proved by Muller (1927), who showed that their "number was so great that through egg counts and effects on the sex-ratio evidence could be obtained of them *en masse*". At moderate doses (Catcheside & Lea, 1945, Demerec & Fano, 1944) the graph relating the logarithm of the percentage of eggs reaching the larval or adult stages to the dose is a linear one. Above 4,000 r the gradient becomes steeper, suggesting that a mixture of "single-hit" and "multiple-hit" effects contributes to the total yield of dominant lethals. The predominant contribution, particularly in the lower dose-range, is single-hit, and dominant lethals involving more than one hit, and so increasing more rapidly than the first power of the dose, become important only at higher doses (Fig 1, A).

The occurrence of dominant lethals is expressed also in the sex-ratio, i.e., the proportion of females relative to males hatching from a batch of eggs. As the x-ray dose increases, the sex ratio declines (Fig 1, B), owing to the extra probability of a dominant lethal being induced in an X-chromosome-bearing sperm as compared with a Y-chromosome-bearing sperm exposed to the same dose. The female-producing X-chromosome is a little larger than the male-producing Y-chromosome, and so presents a larger target in which the dominant lethals may be induced.

Discussion of the nature of the dominant lethals is deferred, except to indicate that the change in the hereditary material does not produce an immediate effect. Eggs which fail to hatch are found to have undergone a number of

nuclear divisions before breakdown occurs (Sonnenblick, 1940).

Amongst the viable offspring of treated male flies, a number carry mutations. The great majority of these are recessive and so do not produce any visible effect immediately, since they are heterozygous. Special measures have to be taken to obtain individuals homozygous for such mutations. The simplest are those for detection of mutations in the X-chromosome, a sex chromosome that is present twice in the female flies and once only in the males. It crosses and re-crosses in heredity in a regular fashion from father to daughter and mother to son. Thus, males will be hemizygous for genes in the X-chromosome, and so will manifest them.

Treated male parents are mated to *CIB* females (Muller 1928), one of whose X-chromosomes carries a cross over suppressor (*C*, actually an inversion), a recessive lethal (*I*) and a dominant marker-gene (*B*, Bar-eye, which is narrower than the normal round eye). Amongst the offspring, females with a Bar-eye are chosen and mated individually with any suitable males, preferably with their X-chromosomes suitably marked with recessive genes. Any one of these F_1 females will have a treated X-chromosome from her father and a *CIB* chromosome from her mother. The *CIB* chromosome will be lethal to male offspring carrying it, so all male offspring of F_1 females will carry only treated X-chromosomes from their grandfathers. Inspection of these males will disclose genes having a visible effect, though their detection will depend on the skill and experience of the observer. On the other hand, if a recessive mutation is lethal, the culture containing it will be marked by a complete lack of male offspring. Such sex-linked lethals are produced by radiations about ten times as frequently as visible mutations. They provide an objective criterion for quantitative work, and have been widely used in experimental studies on mutation-rates. The recessive lethals, of course, represent mutations at a large number of different loci and the grouping together of such a heterogeneous group is justified mainly by the convenience of their frequency.

When viable recessive mutations are to be studied, the attached-X method may be adopted. In this case the treated male is mated to an attached-X female, whose two X-chromosomes are joined together and so are segregated together at gamete formation. Her eggs will be of two kinds, one with two X-chromosomes, and therefore female-producing, and the other without any X-chromosome. The latter, with an X-bearing sperm from the irradiated father, will produce a male in which any visible mutation in the treated X-chromosome could be detected.

These techniques, and others like them, are simple but enormously laborious, since the mutation-rates involved are small even for fairly large doses of x rays. Nevertheless, many facts about the mutation process are well established. In the first place the mutations induced by radiations do not differ qualitatively from those occurring spontaneously. In both cases, too, the mutation-rate differs from one locus to another and from one allelomorph to another at the same locus (Timoféeff-Ressovsky, 1932, 1933). It can be concluded that the genes differ among themselves in stability, the less stable ones undergoing the more frequent mutation. An important point to note is that the radiation cannot determine what particular mutation is produced. Which gene

is activated and what allelomorph is finally formed is a matter of chance. The former depends upon the chance of the target, the gene, being hit, and the latter upon the innate characteristics of the individual locus, in particular, apparently, upon the relative stabilities of the different allelomorphs (Schultz, 1936).

Further, a given gene *A* may be changed to the allelomorph *a*, and the latter on being irradiated changed back to *A*. Such back-mutations, demonstrated first by Timofeeff-Ressovsky (1929, 1930), are important in showing that whatever change is involved in the conversion of *A* to *a* cannot be a loss that may not be restored with relative ease.

The quantitative relationship between the mutation rate and the radiation-dosage, -intensity, -wavelength, etc., has been determined satisfactorily only for the group of recessive sex-linked lethals, though sufficient has been done with visible recessive mutations and with mutation in other organisms to suggest that the results are characteristic. First of all, however, it should be mentioned that the natural mutation-rate in *Drosophila melanogaster* (measured by sex-linked lethals) increases with the age of the tissue tested and with the temperature at which it is kept. Further, it differs from stock to stock and in a few cases may be relatively high. Thus, Demerec (1937) found that the Florida stock gave about 1% of sex-linked lethals, the average of all other stocks being about 0.1%. Thus he found to be due to a recessive gene, located on the second chromosome, which raised the general mutation-rate of all the genes in the organism. This behaviour is to be contrasted with the case found by Rhoades (1941) in maize, where the gene *Dt* increases the mutation rate only of the gene *a*.

The mutation-rate induced by x rays is found to be linearly proportional to the dosage. The frequency of sex-linked lethals induced in *Drosophila* sperm is about 3% per 1,000 r (Schultz, 1936). This rate is independent of the wavelength of the radiation throughout the gamma- and x-ray range up to a wavelength of 2.6 Å. It is independent of the time occupied by the irradiation, i.e. is independent of intensity down to the lowest tested (0.07 r/min) and of whether the dose is fractionated or given in one exposure. Lastly, it is unaffected by temperature and is probably independent of the natural mutation-rate of the particular stock employed. Timofeeff-Ressovsky (1937) should be consulted for full details.

These facts indicate that the induced mutations must be due in quite a direct manner to a single ionization excited in a sensitive volume which may be the gene itself or include the gene or some part of it (Timofeeff-Ressovsky, Zimmer & Delbrück, 1935). The ionization adds considerable energy to the affected gene, and the excited molecule, rendered temporarily unstable, is enabled to slip from one relatively stable chemical state to another. What the precise change may be is unknown, but any change in the gene molecule may be expected to alter the properties of the whole gene and so to be disclosed as a mutation. A simple account of the physical principles involved is given by Schrodinger (1944). Probably not all changes provisionally classed as gene-mutations are intramolecular, but the further consideration of this matter must be left until the grosser effects of radiations on the chromosomes have been described.

Estimates of the sizes and of the number of genes may be derived from mutation data. The best estimates are probably those derived (Lea, 1940, cf. also Lea & Catcheside, 1945)

from a comparison of the mutation-rates induced by x rays and neutrons. These two radiations differ considerably in their relative efficiency in producing sex-linked lethals, the ratio being about 1.6 for x rays neutrons for a given dose measured in terms of ionizations (Zimmer & Timofeeff-Ressovsky, 1938). This leads to an estimated volume of a single gene of about 2.8×10^{-20} cm³, containing about 1,000 atoms, and to there being about 1,860 genes in the X-chromosome of *Drosophila*, each capable of giving X-linked recessive lethals.

Induced Chromosome Aberrations

The chromosomes in a body-cell pass through a cycle of division, mitosis, whereby two nuclei, each an exact reproduction of the parent nucleus, are produced. Before prophase, i.e. in the resting stage, each chromosome divides lengthwise into two chromatids, except at the centromere, and during prophase each assumes a condensed spiral form and becomes coated with nucleic acid. At metaphase, each chromosome moves on the spindle so that the centromeres come to lie in the equatorial plane. At anaphase, each centromere divides, the two halves each with their attached chromatid then moving to opposite poles of the spindle. A new nucleus is then organized at telophase from each of the two groups of daughter chromosomes.

Radiations affect the different stages in various ways. A lengthening of the nuclear-division cycle may be caused, especially by heavier doses. A further physiological effect, shown by adhesion or clumping of the chromosomes, occurs in cells already in division at the time of irradiation (Marquardt, 1938, Koller, 1943). With large doses, excessive clumping may prevent the completion of mitosis. Nuclei at resting, or early prophase, stages at the time of irradiation, although delayed in division, recover and show no adhesive tendency when they reach metaphase. Instead, they may show structural changes. These are due to the production of breaks in the chromosomes, which may be followed by the formation of structural rearrangements resulting from the recombination of the breakage-ends in various ways. This subject has recently been reviewed (Catcheside, 1945) and space permits the description of only some of the manifold changes. The descriptions refer to the appearance of the affected chromosomes at the metaphase of the division-cycle in which the changes are induced.

Structural changes are of two kinds: *chromosome*, where both the chromatids are similarly affected and *chromatid*, where only one of the two chromatids is affected at a given place. The former are normally produced by irradiation during the resting stage, at which time the chromosomes are simple undivided threads. The latter are produced by treatment at the early prophase, when the chromosomes are divided into two chromatids. In flowering plants, the pollen-grains in a given anther and bud develop approximately synchronously. In *Tradescantia*, for example, at 20° C the division-cycle, including a prolonged resting-stage, occupies about 10 days, all the grains in one anther reaching metaphase within a period of less than 24 hours. The material is thus convenient for radiation work in providing a group of cells all approximately at the same stage of mitosis. Chromosome division occurs about 30 hours before metaphase. A change from chromatid to chromosome structural changes is shown by metaphases observed respectively less than, and more than, 30 hours after exposure of pollen-grains to radiations.

Other convenient material is provided by germinating pollen-grains on an artificial medium, and using the nuclear division that takes place in the very thin pollen-tube, 7μ in diameter. This is especially valuable where soft, weakly-penetrating radiations must be studied.

Radiations produce breaks in the chromosomes, and the breaks suffer various fates (Fig 2). A large proportion, estimated at 90%, undergo restitution, the two fragment-chromosomes rejoining in the original way so that no permanent effect can be seen (Sax, 1939, Lea & Catcheside, 1942). This restitution is a matter of inference from intensity experiments to be mentioned later. A further proportion of breaks undergo reunion in new ways. Thus, two breaks, one each in two different chromosomes in the same nucleus, would produce four fragments A_1, A_0, B_1, B_0 . Two of them (A_1 and B_1) have centromeres and two (A_0 and B_0) are without these bodies. Reunion in a new way to produce interchanges could be symmetrical, producing two new viable chromosomes A_1-B_0 and B_1-A_0 , each with one centromere, or could be asymmetrical, producing two defective chromosomes, one (A_1-B_1) having two centromeres and the other (A_0-B_0) having none. Similarly, two breaks within one chromosome could produce symmetrical changes (inversions, cf Fig 5)^a or defective (ring or deficient rod) asymmetrical changes. The defective chromosomes are not permanently functional, since a chromosome without a centromere is inert on the spindle (Fig 3b), while in one with two centromeres there is a complete lack of co-ordination of the two kinetic bodies. The inertness leads to loss of parts of chromosomes from the daughter nuclei and, if this entails the loss of vital genes, the nuclei die. The non-co-ordination of two centromeres leads to chromosome-bridges at anaphase, and ultimately to breakdown and death of the cells. Causes of this type are responsible for those dominant lethals, referred to earlier, that are dependent upon two or more hits.

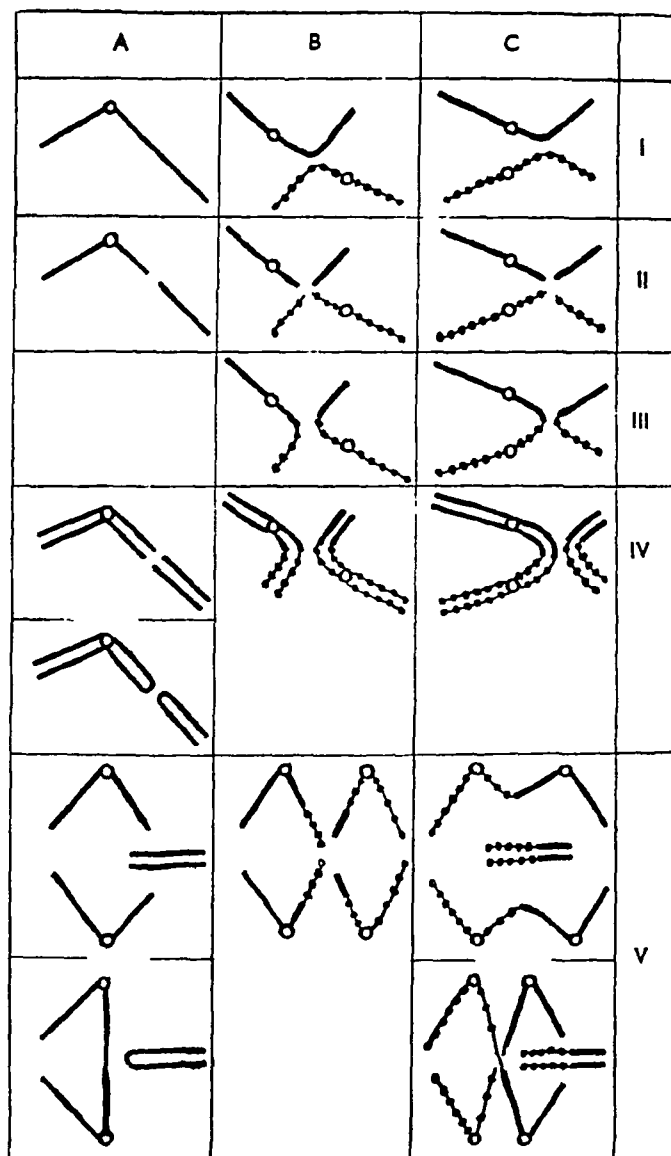
A final proportion of the original breaks neither reconstitute nor undergo reunion in new ways, but instead remain open as chromosome-breaks, the chromosome being present as two fragments, one centric and the other acentric. In some cases the pairs of sister chromatid-ends may undergo sister-union (Fig 4a) and in other cases not. Where sister-union occurs in the centric fragment, a bridge would be formed at anaphase (Fig 3a), leading ultimately to cell-death. Single chromosome-breaks, exhibiting sister-union, account for the major proportion of dominant lethals, namely for those proportional in frequency to the first power of the radiation-dose (Pontecorvo & Muller, 1941, Lea & Catcheside, 1945).

Chromatid-breaks produce a series of analogous chromatid structural changes (simple chromatid-breaks are shown in Fig 4b, and a chromatid-interchange in Fig 3c), some of which are defective, leading to death, and others of which are fully functional and viable. In general, a functional nucleus must have a full complement of genes, and each chromosome must be rod-shaped and have just one centromere. This is not strictly true, since very small deficiencies (absences of one or a few genes) may be viable. Thus, a proportion of the recessive lethals induced in *Drosophila* sperm are actually small deficiencies, as is disclosed by examination of the giant salivary-gland chromosomes (Slizynski, 1938).

The yield of persistent chromosome- and chromatid-breaks

is linearly proportional to dose in the case of x rays (e.g. Sax, 1940, 1941, Thoday, 1942), neutrons (Giles, 1940, Thoday, 1942), and alpha rays (Kotval & Gray, unpublished). The yield is also independent of the radiation-intensity.

FIG. 2. DIAGRAMS OF THE MODE OF PRODUCTION OF SOME CHROMOSOME STRUCTURAL CHANGES



A Chromosome break
I Unbroken,
II Broken,
III Reunion,
IV Metaphase configuration, V Anaphase configuration

(Sax, 1940, Catcheside, Lea & Thoday, 1946). Therefore simple breaks are products of single radiation-hits.

The yields of interchanges and other two-break aberrations produced by x rays diminish with increase of the time over which the irradiation is spread, i.e., with decreasing intensity. These two-break aberrations also increase more rapidly than the first power of the dose. With high intensities, the yields are practically proportional to the square of the dose, at

^a [Figs 3 & 5 are on Plate II facing p. 9—Ed.]

lower intensities the power of the dose is lowered (Sax, 1941). A square law is also found if the dose is varied by varying the intensity at a constant exposure-time. These facts are readily explicable if the two breaks are produced by separate ionizing particles. However, the effects may be distorted by restitution of breaks, unless the irradiation is completed in a short time or the irradiation extends over the same time at all doses. The data also may be employed to show (Lea & Catcheside, 1942) that the mean life of an original break in a *Tradescantia* chromosome is about 4 minutes at 20°C. At lower temperatures its life is probably longer.

With neutrons, the yield of interchanges is independent of the time over which a given dose is spread, i.e., of the intensity, suggesting that a single ionizing particle usually causes both the breaks in the neutron-induced interchanges (Giles, 1943). In agreement with this inference is the fact that the yield of neutron-induced interchanges increases in linear proportion to dose (Giles, 1940, 1943, Thoday, 1942).

X-rays ionize by means of electrons, the ionizations in a path being in clusters spaced apart, except very near the end of the path where the electron has lost most of its energy. Neutrons ionize by means of protons, the ionizations in the path forming a dense column. For a given dose, depending upon the x-ray wavelength and the neutron-energy respectively, about ten to twenty times as many electrons as protons would traverse a nucleus. It is for this reason that, at the low dosages normally employed, neutron-induced interchanges are predominantly one-hit, while x-ray-induced interchanges are predominantly two-hit.

Providing that x-ray doses are measured in röntgen- and neutron-doses in r-units, units which represent approximately equal energy-dissipations in tissue, the ratio of the yields of chromosome-aberrations for equal doses of the two radiations may be taken to be the ratio of the efficiency per ionization of the densely-ionizing particles (protons) in neutron experiments to that of the less-densely-ionizing particles (electrons) in x-ray experiments. This ratio is about 2 to 4 for chromatid- and chromosome-breaks in *Tradescantia* pollen-grains.

The x-ray and neutron data taken together may be used to derive an estimate of the distance apart, at the moment of breakage, of breaks which exchange. The order of magnitude is 1μ (Lea & Catcheside, 1942) and this estimate agrees with those based on other data (Lea, 1946, Catcheside, 1945).

It has already been seen that a *Tradescantia* chromosome

can be broken by a single ionizing particle. If a single ionization were the causative agent, the efficiency per unit dose should be less for neutrons than for x-rays, since those ionizations in excess of the minimum needed to break the chromosome would be wasted. But neutrons are more efficient and this indicates that several ionizations are usually needed to break a chromosome. The probability of a chromosome being broken when a proton traverses it is fairly high, most likely between 0.5 and unity. On the other hand the probability of breakage by an electron is rather low for all of its path except the last densely-ionized quarter-micron (Lea & Catcheside, 1942). It has been estimated that 15 to 20 ionizations represent the minimum amount of energy which, dissipated in a chromosome, is sufficient for the probability of breakage to approach unity. It should be emphasized that these numerical values refer to *Tradescantia* chromosomes and that quite different values may characterize the chromosomes of other organisms.

From a genetical point of view, the use for therapeutic purposes of neutrons and similar radiations with densely-ionized paths instead of gamma rays and x-rays, is to be favoured, for the following reasons. For a given dose, neutrons are more efficient in the production of chromosome structural changes that will lead to the death of the cells and tissues, while they are less efficient in the production of gene-mutations which, produced in gonads, could be harmful to future generations.

Finally, reference should be made to ultra-violet radiations. These can cause excitation but not ionization, that is, they can introduce into genes or chromosomes at one time only a small amount of energy compared with that which may be introduced by x-rays. Ultra-violet radiations produce the usual range of gene-mutations (Stadler & Sprague, 1936, Mackenzie & Muller, 1940), the rate being directly proportional to the dose. The shorter wavelengths, notably those between 2,500 and 3,000 Å approximately, are considerably more effective than slightly longer wavelengths. The ultra-violet is also able to produce chromosome-breaks, though with a remarkably low efficiency (Swanson, 1942), however, there is no certain evidence that interchanges or other two-break aberrations can be produced. From a genetic point of view, the ultra-violet can be extremely useful in providing mutations free from chromosome structural changes, always provided of course that the objects to be treated are small enough to be capable of penetration by the rays.

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THE ACTION OF RADIATIONS ON VIRUSES AND BACTERIA

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The viruses are parasites of bacteria, plants or animals, characterized by their small size and their inability to multiply except in or on the living cells of the appropriate host. The larger viruses, such as vaccinia, are probably correctly regarded as single-celled organisms. The smallest viruses are nucleoproteins, capable of being concentrated and purified by the methods of protein chemistry and in some cases obtainable in a crystalline form. It is evidently not correct to regard these small viruses as cells. From a biological standpoint they may be thought of as naked genes (Muller, 1922). From a chemical standpoint they are to be thought of as large molecules (*macromolecules*) of molecular weight 1-100 millions.

Thus one may expect to find analogies between the mechanism of action of radiations on viruses (at any rate in the case of the smallest viruses), and chemical effects of radiation, and we shall therefore recall the outstanding conclusions of the study of the chemical effects of radiation.¹

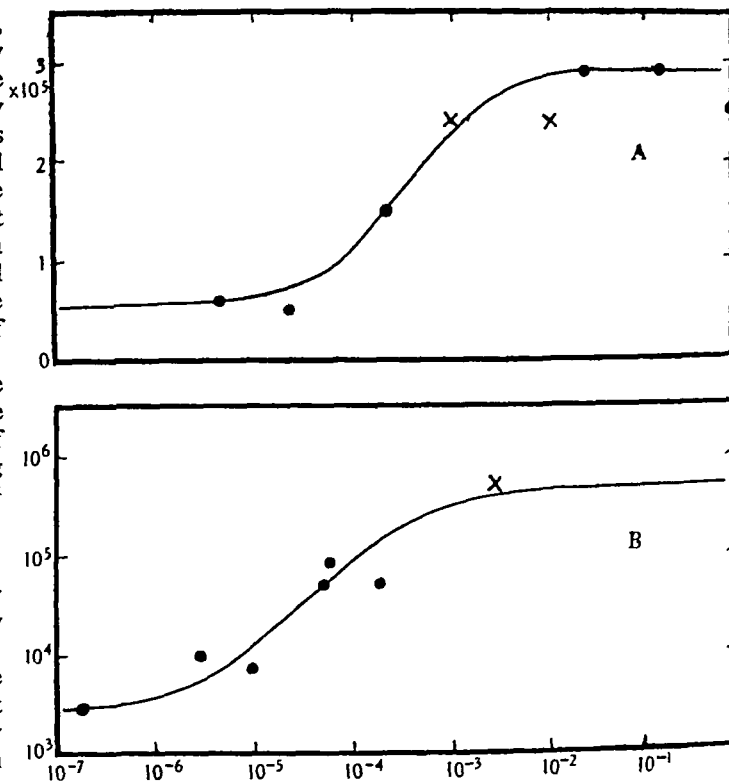
Chemical Effects of Radiation

If a chemical substance is irradiated in the pure state by x rays or alpha rays, the typical result is that approximately one molecule is decomposed for each ionization produced. It appears that the ionization of an atom usually leads to the decomposition of the molecule of which it is a part, a result which is not unexpected in view of the fact that the energy involved in ionization exceeds the binding energy of an atom in a molecule. This (approximate) result has been established for substances in the solid, liquid, and gaseous states, and for substances ranging in molecular weight from about 20 to about 20,000. There are some notable exceptions, but these are probably to be explained on the basis, on the one hand, of recombination of the products of decomposition giving low yields, or, on the other hand, of chain reactions giving enhanced yields.

Many substances undergo chemical change when irradiated in dilute aqueous solution. Among inorganic solutes, reducing agents are oxidized, and oxidizing agents are reduced, while organic solutes are usually eventually converted to CO₂ and hydrogen. These reactions in dilute

aqueous solution take place with doses of radiation much smaller than would be necessary to produce the same percentage chemical change in the solute if irradiated dry, and the number of solute molecules reacting greatly exceeds the number of solute molecules directly ionized by the radiation. Evidently, the ionization of the water is able to lead to chemical change in the solute, and it is believed (Weiss, 1944) that the explanation lies in the production of

FIG 1 INACTIVATION OF VIRUSES IN AQUEOUS SUSPENSION BY X RAYS



Abscissae=concentration of solution in grams per millilitre
 Ordinates=inactivation dose in rontgens
 A Tobacco mosaic virus (Lea, Smith, Holmes & Markham, 1944)
 B Shope rabbit papilloma virus (Friedewald & Anderson, 1941)

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free H atoms and OH radicals following the ionization of the water

Inactivation of Viruses

Both the direct action of radiation (i.e., chemical change due to ionization in the molecule concerned) and the indirect action (i.e., chemical change in the solute molecules due to ionization in the solvent) have been demonstrated in studies

¹ [This subject has been reviewed by Allsopp (1944) and by Lea (1946)]

of the inactivation of viruses by x rays Thus in Fig 1 (Lea, Smith, Holmes & Markham, 1944) it is shown that in sufficiently concentrated solution the dose required to inactivate a given percentage of a virus is independent of the concentration of the solution, indicating that in such solutions the direct action is predominant, but that in sufficiently dilute solutions the dose required to inactivate a given percentage of virus diminishes, showing that in dilute solution the indirect action predominates

Macromolecular Viruses

The study of the direct inactivation of viruses has so far yielded results of greater interest than the study of the indirect action, and we therefore confine our subsequent discussion to the direct action If, on the basis of the results of chemical experiments already mentioned, we are prepared to accept that, in the cases of the macromolecular viruses, every virus particle ionized is inactivated, we are able to use radiation experiments to estimate the size of the virus particle

Suppose that D rontgens is the dose which produces an average of one ionization per virus particle Since 1 rontgen corresponds to the production of approximately 2×10^{19} ionizations per gram, D rontgens corresponds to the production of 1 ionization per $\frac{1}{2 \times 10^{19} D}$ grams This, then, is the mass of the virus particle

This calculation, while satisfactorily illustrating the principle, is somewhat simplified The ionizations produced in an irradiated material are not distributed spatially at random, as the above calculation has tacitly assumed, but are localized along the paths of ionizing particles, as described by Gray* If an ionizing particle passes through a virus particle, usually more than one ionization will be produced in it, the actual number depending on the diameter of the virus and the ion density (i.e., the number of ionizations produced per micron path) of the ionizing particle The ion-density is greater in alpha-ray experiments than in x-ray experiments, and is greater with x rays than with gamma rays We shall therefore expect that the inactivation doses will increase in the order gamma rays, x rays, alpha rays, since a radiation which produces several ionizations in one virus particle, when one would suffice to inactivate it, is inefficient.

Table I shows that the experimental results (Lea & Salaman, 1946) confirm this expectation for a bacteriophage Similar results with plant viruses have been obtained by Lea & Smith (1942)

TABLE I INACTIVATION OF PHAGE S-13
(Phage diameter 16 mμ)

	Gamma rays	X rays	Alpha rays
Inactivation dose in millions of rontgens	0.58	0.99	3.5
Inferred 'target' diameter in mμ	15.5	15.9	16.0

From the experimental inactivation doses one can calculate the "target" diameter, i.e., an estimate of the diameter of the virus based on the hypothesis that an ionization anywhere in the virus particle will inactivate it. The agreement between the three estimates of target diameter and their close approximation to the size of the virus as determined by other methods (centrifugation and filtration) satisfactorily confirms this hypothesis, and incidentally establishes that this bacteriophage is one of the macromolecular viruses

Organism-type Viruses

If we attempt to apply the same type of reasoning to a large virus, we find that the estimates of the target size deduced from experiments with the three radiations do not agree, and are all much smaller than the true size of the virus, as shown in Table II (Lea & Salaman, 1942) It is

TABLE II INACTIVATION OF VACCINIA VIRUS
(Virus diameter 200 mμ)

	Gamma rays	X rays	Alpha rays
Inactivation dose in millions of rontgens	0.080	0.104	0.211
Inferred 'target' diameter in mμ	31	41	70

evident that the hypothesis that an ionization anywhere in the virus particle leads to inactivation is incorrect It is believed that a single atom ionized can inactivate the virus, but it must be an atom, not anywhere in the virus, but in certain radiosensitive constituents of the virus, these constituents comprising only a small fraction of the total bulk of the virus particle This differentiation between radio-sensitive and radio-insensitive constituents suggests a cell rather than a macromolecule, and it is probable that the radiosensitive material is to be identified with the genes The fuller analysis of the radiation data enables an estimate of the number of genes to be made (Lea & Salaman, 1942)

We are thus led to regard vaccinia not as a naked gene, as was appropriate for phage S-13, and the plant viruses, but as a single-celled organism with many genes

Shortly after this suggestion was made, electron micrographs were published (Green, Anderson & Smadel, 1942), showing internal structures in the particles of vaccinia virus, and making it difficult to doubt that the particle of vaccinia is a single-celled organism rather than a macromolecule

It appears from these examples that radiation experiments may be of value in elucidating the nature of viruses Some recent experiments (Lea & Salaman, 1946) on bacteriophages somewhat larger than S-13 suggest that these are very primitive organisms with only 10 or 20 genes

Lethal Mutation in Bacteria

Effects of radiation upon bacteria which have been investigated are, the production of mutations (i.e., permanent changes in form or colour of colony), the reduction of motility, a temporary inhibition of division, and the lethal action, the great majority of investigations being concerned with the last-mentioned effect

What is described as a lethal action in these investigations is the inability of a bacterium after irradiation to give rise to a colony visible to the naked eye when inoculated on a nutrient medium There are, however, distinct differences between the "killing" of a bacterium by radiation, and killing by other agents, e.g., heat or chemical disinfectants Thus, after irradiation, the bacterium which is rendered incapable of giving rise to a colony may still be motile (Bruynoghe & Mund, 1935), may still be capable of respiration (Bonet-Maury, Perault & Erichsen, 1944), and may, when cultured and examined microscopically, show some growth (Luria, 1939) In view of these facts, it is probable that one is dealing with lethal mutation

The internal evidence of the radiation experiments supports this interpretation It appears (Lea, 1940, Lea, Haines & Bretscher, 1941) that a single ionization is able to "kill" a bacterium, but that, as with the large viruses, it does not

* [See BMB 799 in this number —ED]

suffice for it to be produced anywhere in the bacterium. It must be produced in a radiosensitive part which constitutes only a small fraction of the total bulk of the bacterium, and which is, on our interpretation, to be identified with the genes.

Inhibition of Division of Bacteria

Ionization produced in a bacterium but not in the genetical

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material is not without effect. The most striking effect is a temporary inhibition of division. Bacteria grown in a nutrient medium in the presence of a suitable intensity of radiation continue to grow, in the sense of increasing in volume, but fail to divide. In consequence, rod-shaped bacteria grow into long filaments (Lea, Haines & Coulson, 1937).

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QUANTITATIVE HISTOLOGICAL ANALYSIS OF RADIATION-EFFECTS IN HUMAN CARCINOMATA

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Tumours of apparently similar histological type and clinical extent in different parts of the body, or even at the same site, vary considerably in their local response to radiotherapy. Thus, good results are obtained in cases of carcinoma colli uteri, while almost complete failure attends the treatment of carcinoma of the oesophagus. In carcinoma colli uteri, clinical stage¹ 2, 60% of the cases are cured for at least 5 years while 40% of the cases fail to respond satisfactorily.

Attempts to discriminate between the radiocurable and the radioresistant cases by means of histological grading have led to widely divergent results (Heyman, Reuterwall & Benner, 1941; Coutard, 1934; Phillips, 1931). The most anaplastic types of tumour tissue (Borak, 1932; Healy, 1928), as well as the most differentiated types (Blady & Chamberlain, 1944; Evans, Barnes & Brown, 1942; Fricke & Bowing, 1941; Regaud, 1928) have been found to give the best radiotherapeutic results—a finding paralleled by the clinical observation that the highly-differentiated keratinizing epitheliomata of the skin and lip usually respond favourably to radiation-treatment, and that lymphosarcomata and other growths composed mainly of undifferentiated cells react dramatically to radiotherapy, at least locally.

These examples, as well as the rather vague and general statements composing the "radiosensitivity tables" of tumours (Warren, 1941; Desjardins, 1938; Patterson, 1933, 1936), illustrate the difficulties encountered in an analysis of the factors determining the radiosensitivity of individual growths or groups of tumours, and of the likely response to any particular type and dose of radiation.

¹ The clinical stages in carcinoma colli uteri are defined as follows (Heyman, 1938). Stage 1. The carcinoma is strictly confined to the cervix. Stage 2. The carcinoma infiltrates the parametrium on one or both sides but does not extend to the pelvic wall. Stage 3. The carcinomatous infiltration of the parametrium extends to the pelvic wall on one or both sides. Stage 4. The carcinoma involves the parametrium up to the pelvic wall and the bladder.

Although some general principles have been elucidated by radiobiological research, their application to the practice of radiotherapy is handicapped by the heterogeneous collection of nosological entities lumped under the term "cancer" (Ewing, 1941) and also by the essential differences in biological characters and reactions of much of the biological material chosen for experimentation and of malignant cells and tissues.

The study of the local response of various types of neoplastic diseases to radiation can be undertaken only by investigating the actual response of individual tumours to treatment, i.e., by examining serial biopsies taken before, during, and after treatment, and by correlating the histological with the subsequent clinical and pathological findings. It is useless, however, to compare biopsies taken at random with one another, since owing to their localization in the tumour, i.e., whether near the necrotic centre or the well-vascularized growing edge, the specimens from the same tumour may vary as to the proportion of old and young foci included. To obtain comparable results in serial biopsies of an individual case, sections should be taken from the growing edge of the tumour, and in such specimens only the young areas should be chosen for a detailed examination of the reaction of the tumour-tissue to treatment. Young foci alone contribute to the further expansion of the tumour; they possess the greatest developmental potentialities in any given malignant growth, and are best able to react to, and to recover from, the effects of treatment.

If these precautions are taken, reliable and comparable "samples" of young foci in the tumour can be obtained. In a series of about 20 surgical and pathological specimens of various carcinomata, a number of small pieces of tissue equivalent to biopsy sections were taken from the growing edge, comparable young areas were selected in each piece, and their cell-population was classified and counted. The average coefficient of variation from the mean in the various pieces for any given tumour was of the order of 10% (Glucksmann, 1946). Similar observations have been recorded for the histological grading of various biopsies taken from the same tumour (Broders, 1940; Warren, 1931; Patey & Scarff, 1928).

The cellular population of tumours varies with tumour-type. In most epithelial growths, 4 classes of cells can be

distinguished according to their viability. There are 2 classes of viable cells

A The *resting* cells, which are the intermitotic "stock" cells capable both of division and differentiation (depending on the tumour-type). They are relatively small, with a large, often hyperchromatic, nucleus and with little and basophilic cytoplasm

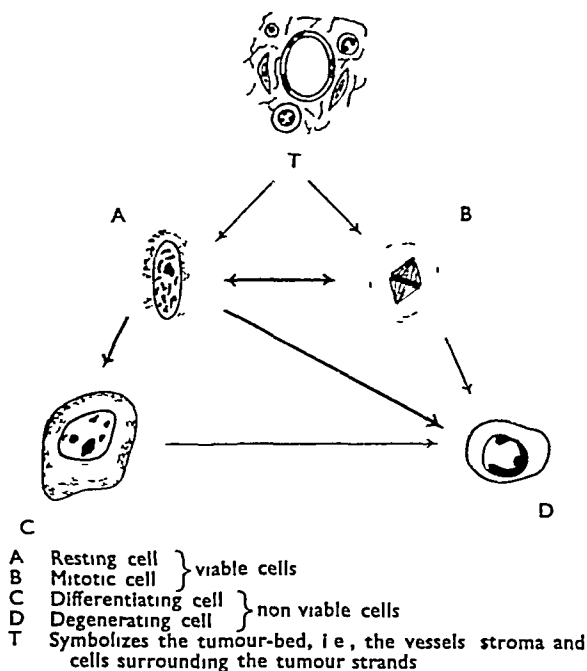
B The mitotic cells, i.e., stock cells actually in division. There are also two classes of non-viable cells

C The *differentiating* cells, which are cells rendered permanently incapable of division by the differentiation of their cytoplasmic structures. Most of these cells are large, with a great amount of differentiated cytoplasm and a relatively small vesicular nucleus

D The *degenerating* cells, which are the cells in the process of disintegration. Their structure changes according to the form of degeneration (fatty, mucoid, parakeratotic, etc.), and to the cell-type from which they are derived

Very immature growths lack the differentiating cells. Fig 1 depicts diagrammatically the main characteristics of these four cell-categories and their relationship with each other, as indicated by the arrows. The cellular composition of the foci is influenced by the tumour-bed, i.e., the vessels, stroma and cells surrounding the tumour-strands, which promotes or inhibits mitosis, differentiation and degeneration

FIG 1 DIAGRAMMATIC REPRESENTATION OF THE FOUR CELL-CATEGORIES FOUND IN MOST EPITHELIAL TUMOURS



Young foci are formed by finger-like projections from tumour-strands, and are characterized by the presence of many mitotic cells, the preponderance of resting cells, and the dissolution of the basement membrane at the growing tip of the projection. The comparison of young foci in serial biopsies is best made quantitatively by classifying and counting all the cells in carefully selected young areas. The

cell-counts are plotted as percentages against time after beginning treatment, and thus a chart is obtained of the response of a given tumour to a given type of treatment (Glucksmann, 1941)

Changes in the cell-population of young tumour-foci are the result of direct and of indirect effects of radiation. The direct effects concern mainly resting and dividing cells. After a transient mitotic inhibition, resting cells may break down on attempting division, they may differentiate according to their type and potentialities, or they may disintegrate immediately after exposure. Enlargement of resting cells often follows an irradiation.

After a period of mitotic inhibition, cell-division may be resumed with varying degrees of abnormality. A sufficiently high dose of radiation delivered at a high intensity may cause the immediate disintegration of mitotic cells. The direct effects of radiation thus cause a diminution in number of resting and dividing cells and promote the "ageing" of cells and foci. Apart from some increase in cell-size, the effect of radiations on cells in the early stages of differentiation has not yet been precisely determined.

The indirect effects of radiation are due to the interference with the vascular and connective-tissue system of the tumour, and to the induction or exacerbation of inflammatory reactions. Insufficient blood-supply affects the process and the incidence of cell-division, and may cause the disintegration of cells. The inflammatory reaction leads to the infiltration and the breaking up of tumour-strands by round cells, followed by the formation of fibrotic scars.

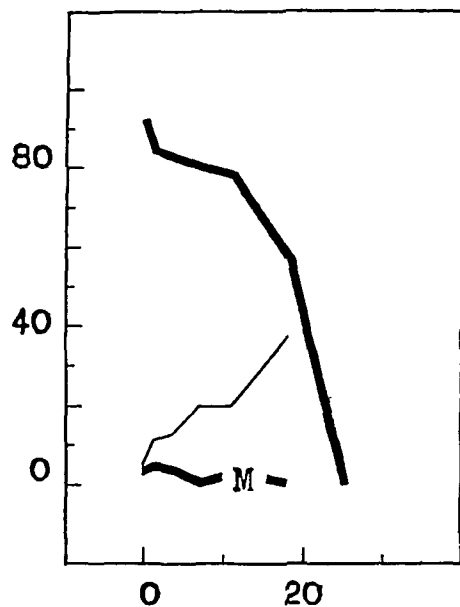
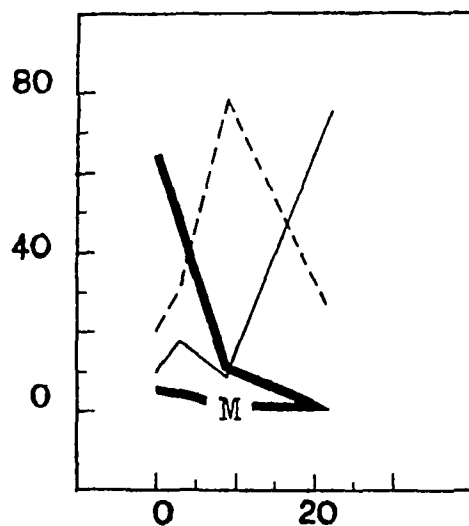
The aim of radiotherapy in malignant disease is to convert viable into non-viable cells, i.e., to induce the breakdown of dividing cells and to prevent cell-division, to cause the immediate disintegration of resting cells, or their permanent sterilization by differentiation. The observed radiation-changes in malignant growths vary according to the tumour-type and the dose, dose-rate, and time-interval between a given dose and the biopsy excision. Some types of reaction of young foci to radiotherapy are illustrated in Fig 2-5.

Fig 2 represents the reaction-chart of a basal-celled carcinoma of the temple treated by a dose of 3,200 r of x rays given in 13 days. Cell-counts made in selected young foci of serial biopsies show a diminution and finally a disappearance of mitotic cells and an initially slow and later rapid disintegration of resting cells. Clinically the lesion responded well to treatment and remains healed. This case illustrates the response of undifferentiated tumour cells to radiotherapy by mitotic inhibition, degeneration of mitotic cells, and the disintegration of the "aged" resting cells. A few of the resting cells were apparently killed directly by the radiation.

The charts in Fig 3-5 refer to cases of epithelioma (carcinoma) coli uteri, clinical stage 2, treated by radium insertions on days 0, 7 and 21 by a modified Stockholm technique.

Fig 3 shows the reaction-chart of a favourably-responding tumour which was an epithelioma with keratinized foci Broders grade² 2. The malignant tissue reacts rapidly to treatment, with a marked increase in number of differentiating

² Broders's histological grading of malignancy is based on the degree and extent of cell de-differentiation. The least malignant, i.e., the most differentiated form constitutes grade 1 and consists of 0% to 25% of de-differentiated cells. Grade 2 contains 25% to 50%, grade 3 50% to 75% and grade 4 75% to 100% of de-differentiated cells.

FIG 2. REACTION-CHART OF
BASAL-CELLED CARCINOMAFIG 3 REACTION-CHART OF
EPITHELIOMAFIG 2-5
Graphs showing cell-counts in young foci of
serial biopsies taken from the growing edge
of tumours before and during radiation
treatmentAbscissae=time in days
Ordinates=cell counts %

Viable cells

— resting cells

--- M --- mitotic cells

Non-viable cells

- - - differentiating cells

- . - . - degenerating cells

FIG 4 REACTION-CHART OF EPITHELIOMA

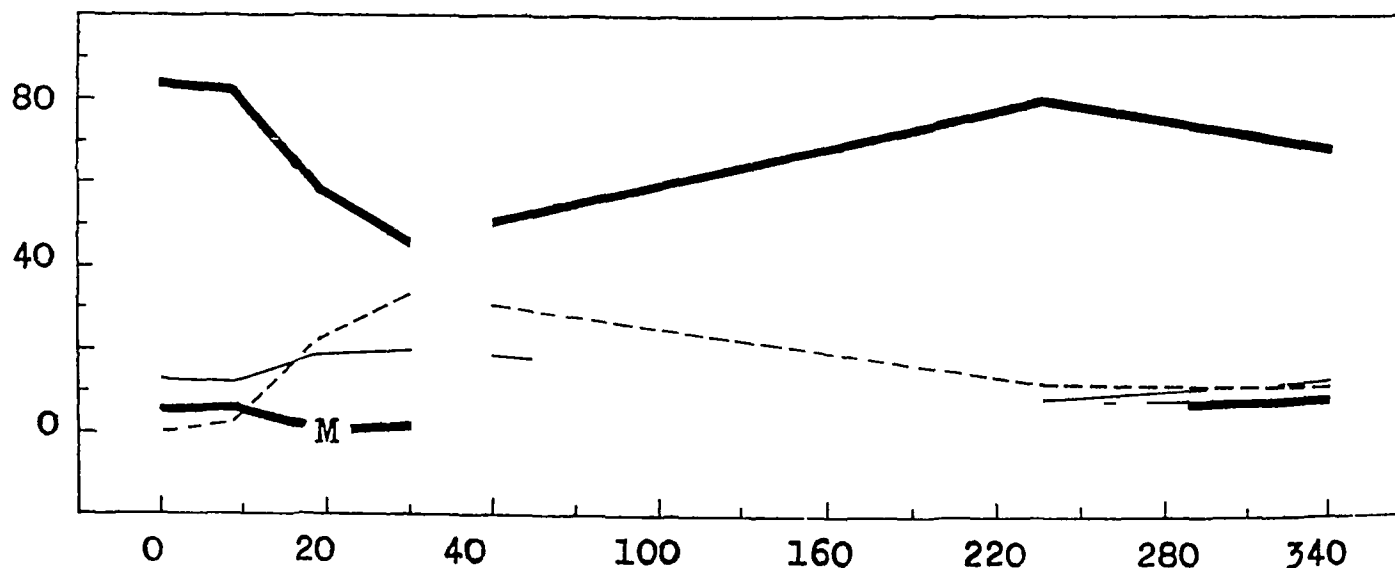
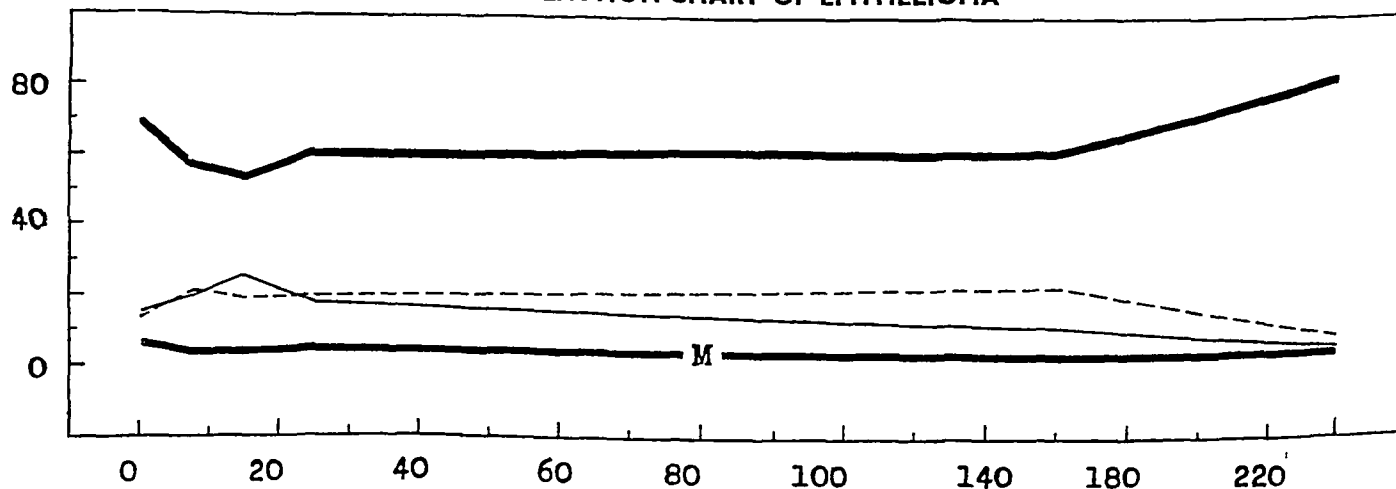


FIG 5 REACTION-CHART OF EPITHELIOMA



cells which subsequently disintegrate. The mitotic and resting cells decrease in number and disappear. Clinically, healing of the lesion was noted after 3 months and the patient has remained well and symptom-free for 5 years.

Fig 4 represents the reaction to treatment of another epithelioma of the cervix uteri, clinical stage 2, Broders grade 3. The effect of 3 radium-insertions in this case is approximately equal to that of a single insertion in the case of Fig 3, i.e., there is some reduction in the percentage of viable cells and a corresponding increase in the percentage of non-viable cells. This change does not, however, lead to the complete disappearance of viable cells, and the tumour tissue is thus able to recover from the radiation-effects. This chart indicates a merely temporary inhibition of growth of the tumour-tissue. Clinically, the lesion appeared to heal and there was no evidence of growth 6 months after treatment. The tumour reappeared later in the treated area and caused the death of the patient 16 months after the beginning of treatment.

Fig 5 illustrates the reaction to treatment of another epithelioma of the cervix uteri, clinical stage 2, Broders grade 3. There are only minor fluctuations in the cell-counts, and the chart indicates the persistence of tumour-activity almost unchanged by the type of radiation-treatment given. Clinically, however, the lesion appeared to be healed after 3 months. Three months later a "recurrence" of the tumour in the treated area was diagnosed, and the patient died 6 months later with growth in the treated area and with extensions.

In these 3 illustrative cases of carcinoma colli uteri (Fig 3-5) the lesion appeared to be healed 3 to 6 months after treatment although in 2 of the cases the histological-reaction chart (Fig 4 & 5) indicated the persistence of active tumour growth. In both these cases the tumour recurred subsequently. In a series of 150 cases of carcinoma colli uteri, 26 cases reported clinically satisfactory during the first 4 months after treatment developed a "recurrence" during the succeeding 8 months, in each case the reaction-chart, obtained within 3 weeks of beginning treatment, indicated the persistence of tumour-activity (Glucksmann & Spear, 1945).

The histological findings based on a quantitative analysis of the cell population of young foci in serial biopsies seem to give a reliable and early indication of the likely outcome of radiotherapy in individual cases, whereas clinical healing is useful as criterion in the evaluation of therapeutic results only if it persists for the conventional period of 5 years. Practically all tumours shrink to some extent under treatment—presumably owing mainly to the damage inflicted on parts of the vascular system supplying the growth and to its sequelae—and this shrinkage allows of the restoration of the normal anatomical configurations in spite of the persistence of active, microscopic tumour-foci. Decrease in tumour-volume of itself is no real measure of the efficiency of therapy. As with surgery, radiation-treatment of cancers aims at the complete elimination or sterilization of viable tumour-cells, and a 90% success of therapy is ultimately a failure. The histological-reaction charts (Fig 2-5) are measures of tumour-activity, and bear no relation to the actual size of the tumour at the time of the biopsy-excision.

The persistence of active microscopic tumour-foci in apparently restored sites is the reason why, shortly after

treatment, the histological findings may be at variance with the results of clinical examinations. Agreement becomes, however, closer with the lapse of time. For example, in the series of 150 cases referred to (Glucksmann & Spear, 1945) there was agreement between histological and clinical findings in only 50% of the cases after 4 months and in 80% of the cases 2 years after treatment.

Apart from showing within 3 weeks of beginning treatment whether or not the aim of therapy is being realized, the histological analysis gives some useful information about the way in which the therapeutic results are obtained. In cases like that of Fig 2, the successful treatment is due in particular to the "mitotic" effect of radiation, i.e., to mitotic inhibition and to disintegration of dividing cells, this prevents the further formation of resting cells which consequently age and having reached the limits of their short span of life, die. Some resting cells are also killed immediately by the radiation and others fall victims to unfavourable conditions in the tumour-bed induced by radiation.

In epitheliomata like that of Fig 3, the mitotic and vascular effect of radiation is supplemented by the "differentiation" effect, i.e., resting cells are forced (either directly or secondarily to mitotic inhibition) into differentiation, and are thus sterilized. This observation suggests that the capacity for differentiation in resting malignant cells and its stimulation by radiation may be one of the factors in the "radiosensitivity" of tumour-tissue.

An indication of the capacity for differentiation of the tumour-tissue—though not of its reaction to radiation—may be gained from the presence or absence of differentiated foci in the pre-radiation biopsy of the tumour. Histological classification as to degree of differentiation of such specimens shows that, clinical conditions and treatment-methods being equal, the results of radiotherapy tend to be more satisfactory in the cases with more-differentiated tumour-tissue (Glucksmann & Spear, 1945). The physical factors of radiation, such as time, dose, dose-rate and type of ray, which are most likely to elicit differentiation in cells with such potencies, are as yet little known and understood. It appears feasible that favourable results may be obtained with changes in technique in those groups of tumours which so far have proved refractory to treatment.

There are various limitations in the application of the quantitative histological method of analysis of radiation-effects in individual cases of malignant disease. Thus conclusions about a favourable response to treatment must be limited to the reaction of the growth in the treated area, presupposing that the radiation-energy was fairly uniformly distributed in this area. In spite of cures in the treated area the clinical issue may, of course, be compromised by the presence of untreated metastases, or even by fatal haemorrhages due to radiation-damage inflicted on the vascular apparatus. Certain types of cancer are systemic diseases with local manifestations, and obviously the cure of one of these manifestations cannot prevent the formation of new ones which may even arise in neighbouring precancerous lesions.

Conclusions

To summarize, the quantitative histological examination of serial biopsies of human tumours provides a useful guide in the evaluation of the therapeutic result in individual cases.

As a research method, it facilitates the analysis of the "radio-sensitivity" of an individual growth, makes possible the study of the factors influencing the response of a given tumour to a given type of treatment, and provides a basis for the understanding of radiation-effects on tumour-tissue of different types and for the better knowledge of the natural history of malignant diseases. The combination of such

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knowledge with relevant data contributed from radio-biological research is the necessary requirement for progress in the radiotherapy of neoplastic diseases. Ewing (1940) has pointed out that "there is little significance in discussing the curability of cancer as a whole. The discussion has real meaning only when the different types of cancer are considered separately as nosological entities."

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THE MEASUREMENT OF RADIATION

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I INTRODUCTION

A comprehensive discussion of the whole of the vast field which might be implied in the above title is clearly out of the question here, so the present remarks will be arbitrarily confined to the subject of ionizing radiation, around which most interest is centred in the present context, leaving aside entirely the question of ultra-violet, infra-red, and "short wave" radiations, which are of no less importance in biology and therapy.

By "ionizing radiations" we mean those types of radiation which in their interaction with matter are able, by virtue of their high intrinsic energy, actually to disrupt the individual atoms or molecules by the splitting-off of an electron. The electron thus set free quickly attaches itself to some other molecule, and so, dispersed among the normal electrically-neutral molecules, there appear positively- and negatively-charged molecules or clusters known as ions, which may exist independently in the medium for considerable lengths of time, and endow it with the property of electrical conductivity.

If left to themselves, the ions will gradually neutralize each other, but the exact status quo may not be restored, for obviously the chance that various types of atomic and molecular rearrangement, i.e. chemical change, will occur is considerable. It is believed that such changes caused by ionization are the more immediate causes of the biological effects produced. On the other hand, by the application of sufficiently large electric field, it may be possible, in a gas at any rate, continuously to remove the ions to the two elec-

trodes almost as fast as they are produced by the ionizing radiation, before any appreciable recombination can take place. The electric current in such circumstances is called the "saturation current" and, in most cases arising in practice, it is very minute.

Examples of ionizing radiations are the electromagnetic type as in x rays, and the gamma rays from radioactive substances, the swift electrons in cathode rays and the beta rays from radioactive substances, protons, alpha particles, etc., and neutrons, all of which have a similar ultimate mode of action in biology.

The necessity for some system of measurement of radiation in biological and therapeutic studies need hardly be emphasized, but in practice it has proved an exacting pursuit, aptly illustrating Kelvin's historical remark that no phenomenon can be understood till it can be measured and expressed in numerical terms. The difficulties lie in deciding on, and realizing practically, a suitable measure of "amount" of radiation, and arise partly from that common feature of the radiations which is most obvious, namely, their power of penetrating matter, and partly from the very small amounts of energy involved. For example, the total amount of energy communicated to the tissues in a typical complete therapeutic treatment would suffice only to augment the temperature of the mass by about one hundredth of a degree Centigrade.

To keep our discussion to a reasonable length, it will be necessary to confine ourselves to what is by far the most important method in this branch of radiation measurement, the ionization method, and to concentrate on the principles involved, omitting detailed descriptions of techniques. In an adequate historical account, considerable interest would attach to the photographic method of measurement¹, but here, we merely remark in passing that it has been developed as a precision technique only in certain rather restricted fields, though it remains a very useful and often simpler alternative to the ionization method when high accuracy is unnecessary—for example, in the recording of stray radiation

¹ Some of the earliest dosimetry was done by finding the time required to photograph a hand!

in questions of staff protection. Other methods, such as chemical methods, change of colour or fluorescence of salts, selenium cells, etc., proved unsatisfactory and are of historical interest only.

Again, comparative studies have been made by using some standard biological test-material, for example, *Drosophila* eggs, but it is clear that far greater importance attaches to the more fundamental problem of relating biological effects to the radiation producing them, evaluated in precise physical terms. The radiations hitherto most commonly met with are α rays and the gamma rays of radium, and they will of necessity occupy most of our attention.

II α AND GAMMA RADIATION

a Quantum Character and Interaction with Matter

These radiations are different examples of essentially the same type of radiation, and it may not be out of place to state briefly some of the most important facts relating to their interaction with matter. The radiation is electromagnetic in character, propagated with the speed of light. For our purpose it is best to concentrate on the quantum character of the radiation, that is, the energy of the beam of radiation is concentrated in discrete units rather like a hail of bullets, the amount per unit being given by Einstein's equation

$$E = h\nu$$

where h is Planck's universal constant, and $\nu = \frac{c}{\lambda}$, where ν , λ and c are the frequency, wavelength and velocity of the radiation, the latter also being a universal constant. These quanta or photons interact with matter in several different ways.

i "Unmodified," or Thomson scattering. A quantum is merely deflected from its course without loss of energy by an individual electron, so that a unidirectional beam becomes diffuse. Unmodified scattering is not of great importance in our present considerations.

ii "Modified," or Compton scattering. A quantum "collides" with an individual electron, projecting it in one direction while itself rebounding in another (and related) direction, with a reduced energy (and therefore longer wavelength) depending on the direction taken. The detailed theory of the fractions of the energy of an incident beam of quanta imparted to the recoiling electrons and scattered quanta and their angular distribution has been given by Klein and Nishina, and is in very good agreement with experiment. The phenomenon is only slightly affected by the atomic number of the substance.

iii Photoelectric absorption. A quantum is absorbed completely by the atom as a whole. Nearly all the energy* is expended in extracting an electron from the atom and endowing it with kinetic energy. The phenomenon is practically completely described by theoretical and empirical relations. The fraction of energy of the incident beam converted reckoned per electron, is approximately proportional to the cube of the atomic number, i.e. the effect is much more pronounced in "heavy" than in "light" elements. Apart from certain well-understood discontinuities, the energy conversion varies roughly as the cube of the wavelength of the radiation, i.e. it becomes less important for higher quantum energies.

* A very small fraction is expended in atomic recoil.

iv Various nuclear effects. Production of electron and positron pairs and nuclear disintegrations becomes of importance only for quanta of high energy. These effects are practically negligible even for radium gamma rays. They vary with the atomic number of the nucleus.

These processes all contribute to a removal of quanta from a beam, the fraction of the energy removed is termed an absorption coefficient, and may be reckoned per electron, per unit mass, or per unit volume of the material.³ Some of the energy is imparted to fast electrons, the so-called "corpuscular emission". It is these swift secondary electrons which actually ionize and excite the atoms and molecules of the medium.

b The Concept of Quality

The "quality" of a beam of radiation refers to its intrinsic characteristics such as wavelength, or quantum energy. It may be investigated exactly by spectrographic methods (crystal diffraction) or by measurements of the energy of the secondary electrons produced in matter. A quick practical method, particularly useful for approximate results with heterogeneous beams, is to measure the absorption or attenuation of the radiation in some suitable standard substance, from which an average or effective wavelength of the radiation may be estimated. Thus it is usual to quote the half-value layer (HVL) of a given beam of x rays in aluminium, or copper, i.e. the thickness of material required to reduce the "intensity" (dose-rate, see below) to one half.

By suitable developments of these principles, it is possible in some cases to form an estimate of the effective wavelength of the diffuse radiation produced during the passage of a beam through matter. Thus the measurement of "quality" is achieved by the application of familiar physical ideas and need not be dealt with here in detail. It may be mentioned in passing that the particular aspect of quality of greatest biological significance is the spacing of the ions along the tracks of the ionizing particles, the "ion density". As the energy of the ionizing particle becomes less, the shorter the interval between successive ions.

c The Concept of Quantity or Dose

When we come to the question of "quantity," it is necessary to break new ground. Normally, "amount" of radiation is expressed in terms of intensity, defined as quantity of energy flowing through unit area of the beam per unit time but any arbitrary measure of "amount" related to this however indirectly, would serve. Obviously, it is desirable to choose as a measure that physical quantity which stands in the closest relationship to the biological effects produced by the radiation. By making a shrewd choice in this matter the interrelation of physical cause and biological effect will not be obscured by a long chain of essentially irrelevant intermediate processes.

There is general agreement that the key quantity is the ionization produced in the biological substance. With a few exceptions, however, it has for technical reasons proved quite impracticable to measure the actual ionization in a solid or liquid, but a quantity which is almost as acceptable as ionization, as a measure of the radiation, is the energy communicated to the medium. The reason for this is that the proportion of this energy which goes to the production of

³ The absorption coefficients of any one atomic type are practically independent of its state of chemical combination.

ionization is probably independent of the quality of the radiation—this is certainly almost exactly true for air⁴ and thus the ionization is known apart from a constant of proportionality characteristic of the medium⁵. In actual fact, however, the direct measurement of the energy communicated to the medium is also well-nigh impossible because of the minute amount required even for the most extreme biological effects. We shall see later how it is possible to derive this energy from other measurements.

d The Rontgen

With these general ideas in mind, it is easy to see why, in actual historical fact, the ionization produced in air came to be adopted as a measure of radiation, partly as a matter of expediency on account of the relatively simple technical problems, and partly because it was realized that, on account of the general similarity of the atomic types in air and tissue, the energy conversion of x and gamma radiation in these two media would be roughly parallel for all qualities⁶.

Thus Villard in 1908 first suggested a unit based on air-ionization—that quantity of radiation which, by ionization, liberates one electrostatic unit of electricity per cubic centimetre of air under normal conditions of temperature and pressure. Much work remained to be done, however, before a satisfactory realization of the idea underlying this proposal was possible. Much of the difficulty lay in the phenomenon of the "wall effect" of the ionization chamber. The radiation causes the emission of secondary electrons from the walls of the chamber, so that the observed ionization in the air of the chamber, instead of depending uniquely on the radiation itself, is determined by a complex set of factors such as the nature of the walls and the size of the chamber. The surmounting of these difficulties and the development of the theory of the ionization chamber will be referred to later.

The necessity for general agreement on a satisfactory unit became ever more pressing, and in 1923 the first steps were taken by the British Rontgen and Physical Societies. Discussions followed with the first international congress of radiology in 1925, and finally matured at the second international congress in 1928. The unit of x -ray quantity, or dose, called the "röntgen" (symbol, r) was defined as "the quantity of x radiation which, when the secondary electrons are fully utilized, and the wall effect of the chamber is avoided, produces in 1 cc of atmospheric air at 0°C and 760 mm mercury pressure, such a degree of conductivity that one electrostatic unit of charge is measured at saturation current".

e The "Free-air" Chamber

In order to make measurements in accordance with this definition, a rather special technique is necessary, namely, the use of the "free-air" chamber. A narrow beam of radiation, accurately defined by a diaphragm, is passed through a large chamber of air and out through a hole in the far end, completely avoiding the walls. A uniform electric

field between two parallel plates on either side of the beam collects the ions as fast as they are formed. A measurement is made of the current to a small separately-insulated section near the middle of one plate. The length of this section and the cross-sectional area of the beam define an effective "ionized volume" of air, so the ionization current per cubic centimetre of air may be deduced—that is, the dose-rate in röntgens per second⁷.

The details of such a measurement call for very careful attention, but an intercomparison of the various national standards in 1931 showed that there was agreement to within $\frac{1}{2}\%$.

f The "Thimble" Chamber

Parallel with these developments was the gradual emergence of the small ionization chamber, the so-called "thimble" chamber, the theory of which will be referred to below. The "free-air" chamber is clearly a special laboratory-instrument and, further, is inapplicable to the measurement of the diffuse radiation produced when a beam enters matter. It was realized that the difficulty of the wall-effect of a "thimble" chamber would not arise if the material of the walls themselves behaved like air in its interaction with the radiation. It was hoped that a chamber with walls, the effective atomic number of which, in relation to the photo-electric process, was the same as that of air, would give readings exactly paralleling those of the "free-air" chamber for any quality, i.e. that it would be "wavelength independent". Unfortunately this is not strictly borne out in practice, the precise reasons for the discrepancy still not being fully understood.

However, by suitable choice of such factors as the materials of the wall and the central electrode, the wall-thickness and chamber-size, it has proved possible to produce empirically chambers having a sufficiently close response to that of the "free-air" chamber, and the chambers can be calibrated to read directly in röntgens. The precise quality of the very heterogeneous radiation within a given medium is not in general calculable, or even easily measurable, and so it is of great practical importance that the "thimble" chamber to be used should not require an appreciable quality-correction. It is clearly also of importance that the chamber should be as small as possible in order to define closely the precise location of the measurement, and that it should be sufficiently transparent to the radiation not to produce an appreciable "shadow".

g Dosimeters

"Thimble" chamber dosimeters may be used in the direct measurement of dose-rate or of dose. In the first case, the actual ionization current is determined by measuring the voltage-drop across a high resistance. In the second case, the ionization current is allowed to charge a condenser, the final voltage of which is a measure of the total dose. In either case, a sensitive voltmeter of the electrometer type is likely to be required. All insulations must be of very high standards, for the currents dealt with are very small, for example, the relatively high dose-rate of 1 röntgen per second produces in a chamber of 1 cm³ volume a current of only one three-thousandth of a microampère. In some instruments, the ionization chamber, electrometer system, and recording mechanism are permanently connected, often with

⁴ About half the energy goes to the production of ionization the rest being expended in excitation.

⁵ In one of the very few investigations of a liquid in this case carbon disulphide Taylor has shown that the proportion of energy expended in ionization is not greatly different from that expended for air.

⁶ If the average atomic numbers of two media are fairly close then the relative importance of any one type of energy-conversion process (Compton photo-electric etc.) will be similar in the two media and so the variation of the gross energy conversion with quality will be similar for the two media.

⁷ If the cross section of the beam at the defining diaphragm is used in the calculation of the ionized volume then the dose rate so deduced refers to the strength of the beam at the diaphragm.

long cables, so that readings may be taken at relatively long distances from the point of measurement

In the condenser-dosemeter, the ionization chamber is entirely separate from the electrometer and measuring devices during exposure to the radiation. The ionization current serves partially to discharge the originally fully-charged capacity formed by the chamber itself, and any added condenser. The charge lost is thus a measure of the dose. This type of chamber is particularly suitable for direct use in body-cavities during therapeutic treatment. Very compact units have been developed, with small ionized volume and large electrical capacity, so that large doses can be measured. Chambers are now being used inside needle-like sheaths which can actually be inserted into the tissues, during treatment. Condenser-chambers have the advantage that several may be used simultaneously, so that an extended field of radiation may be rapidly surveyed. Another particularly suitable application is the so-called "protection chamber" for recording the dose received by workers owing to small amounts of stray radiation.

h The Measurement of Gamma Rays in Röntgens

To turn again to the more theoretical side of radiation measurement, the desire to measure gamma radiation in röntgens has resulted in great advances in the understanding of the ionization chamber and of the energy-exchange between radiation and matter generally. Special interest attached to the problem of the gamma radiation from radium, in particular the dose-rate produced by 1 mg of radium at 1 cm, when filtered by 0.5 mm of platinum (to cut out the primary beta radiation)—the so-called specific gamma-ray dose-rate of radium.

As early as 1931, Mayneord estimated this quantity from the known energy-output of the radium gamma radiation (obtained by calorimetric measurements by Ellis and Wooster), and from the known absorption coefficient of air, to be 8.7 r/hour, and a measurement with a "thimble" chamber calibrated by comparison with an x-ray dosimeter gave 9.2 r/hour, in reasonable agreement. Mayneord, in 1933, further estimated this quantity from Eve's constant⁹ as 8.9 r/hour. But at the same time attempts to measure the specific gamma-ray dose-rate directly with "free air" chambers led to values of only about one-third of the above, so that there was considerable fear that the expression of gamma-ray quantity in röntgens was without meaning.

This disharmony was resolved by Kaye & Binks in 1937, who showed conclusively that on account of the large range in air of the secondary electrons produced by the gamma radiation, the dimensions of the "free-air" chamber need to be very much greater than in the case of x radiation, for the equilibrium intensity of the secondary electrons to be reached, and for their energy to be fully utilized in producing ionization. The current obtained from the "free-air" chamber with gamma radiation no longer originates in the simple "ionized volume" as in the case of x rays but, provided the dimensions are large enough, a geometrical argument shows that full compensation exists and the same simple calculation is valid. Kaye & Binks found a value of approximately 8.0 r/hour for the specific gamma-ray dose-rate of radium.

⁹ Eve's constant is the number of ion pairs per second per unit volume produced in air at 1 cm from the quantity of radium C in equilibrium with 1 g of radium.

Friedrich provided further confirmation in 1938 by measuring the ionization in a small thin-walled chamber suspended in air in the centre of a large hall, so that it was influenced solely by the secondary-electrons (in equilibrium) produced in the air. In this way, a value of 7.8 r/hour was found for the constant. Lastly, Taylor & Singer in 1940 made very precise measurements with a "free-air" chamber operated at ten atmospheres' pressure, in order to reduce the size, and obtained the figure 8.16 r/hour. All doubts as to the legitimacy of measuring gamma rays in röntgens have thus been finally dispelled.

i True Energy-Absorption and the Theory of the "Thimble" Chamber

Of greater fundamental physical importance, however, was the work on the "thimble" chamber method of measurement, referred to several times above. The essence of this idea was provided in 1911 by Bragg, re-discovered by Fricke & Glasser in 1925, and again independently by Gray in 1929. Innumerable other workers have made contributions of various kinds, but it was only after Gray's detailed treatment that an adequate insight into the problem was attained, and the idea of radiation-dose advanced a stage further than the röntgen unit.

It must be borne in mind that the röntgen is solely a measure of exposure to radiation—it merely describes what the beam of radiation will do in air, and not what it will do in any other medium, although it gives a good approximate guide to the latter in the case of light elements, such as occur, for example in tissue. Furthermore, the energy absorption in a medium other than air cannot in general be calculated from the röntgen dose by correcting with the ratio of the absorption ("energy conversion") coefficients of the medium and air, because normally the quality of the radiation, on which these coefficients depend, is unknown.

Gray's theory removes this element of vagueness, for it enables the *actual energy* communicated to any medium to be deduced from *measurements* of the ionization produced in a small gas-filled cavity in that medium. If E is the energy communicated to the medium per unit volume, J the ionization per unit volume of the gas-filled cavity, and ρ the ratio of the rates at which a secondary particle loses energy in the medium and in the gas of the cavity, and W is the average energy expended by the secondary particles in producing an ion pair in the gas of the cavity then

$$E = \rho W J$$

The detailed derivation and exposition of this relationship, called by Gray the "principle of equivalence" must be sought in the original publication. There are certain restrictions: (i) the fraction of their energy lost by the secondary particles in crossing the cavity must be negligible⁹, (ii) the cavity must be surrounded on all sides by a thickness of the medium at least equal to the maximum range of the secondary particles, (iii) the strength of the beam of radiation must be sensibly uniform over the cavity¹⁰.

⁹ Restriction (i) is unnecessary if the gas in the cavity is of the same constitution as the walls.

¹⁰ Strictly, it must be sensibly uniform throughout all that part of the medium from which secondary particles can reach the cavity. One particular application of the theory is to determine the specific gamma ray dose rate of radium by measurements with a thimble chamber. For a chamber wall of light elements for example graphite the energy-conversion of this quality of radiation is the same (per electron) as for air. Thus by correcting the observed ionization in the chamber according to the quantity ρ (which is known) the ionization in a true air wall chamber is deduced. The specific gamma ray dose-rate of radium determined in this way is very close to 8.4 r/hour.

In some cases, particularly in the ordinary x-ray region, the behaviour of small "thimble" chambers appears to deviate from the foregoing analysis. On general grounds, it may be presumed that the conditions attaching to the principle of equivalence have not been fulfilled in these cases. Although the deviations are not usually large, and the use of such chambers can be avoided in practice, yet the effects are of considerable intrinsic interest and have received much attention.

j The Re-definition of the Rontgen and the Extrapolation Chamber

With the development of the work on the measurement of gamma radiation, the need was increasingly felt for a re-wording of the definition of the rontgen. One reason was the desirability of admitting the "thimble" chamber, previously excluded by the clause about avoiding wall-effect, as a valid device for measuring in rontgens, but more important was the practical necessity to disentangle the fundamental dose-unit from the complexities surrounding the actual ionization in air in certain conditions.

For example, because of the relatively long range of the secondary electrons produced by gamma radiation, the ionization at any point may not bear any simple relation to the strength of the radiation-beam there, i.e., the energy actually communicated to the medium at a given point may not come from energy-conversion of the radiation at this point, but from various points, depending on the geometry of the environment. Normally, a complete compensation exists, and the energy converted is equal to the energy communicated to the medium at the same place, but this will not strictly obtain (i) if the strength of the radiation varies appreciably over a distance comparable to the maximum range of secondary particles reaching the point or (ii) in the region of a boundary between two different media. The question in such cases, therefore, is whether "energy conversion" or "energy communication" is to be adopted as the measure of dose. From the point of view of biological effect, the latter quantity is the important one, while the former is, logically speaking, irrelevant, but far simpler to deal with in practice, and it was adopted at the fifth international congress of radiology in 1937.

"The rontgen shall be the quantity of X or gamma radiation such that the associated corpuscular emission per 0.001293 gramme of air¹¹ produces, in air, ions carrying 1 electrostatic unit of quantity of electricity of either sign."

This is effectively the same as the 1928 definition with certain ambiguities removed.

In a detailed consideration of the biological effects of radiation in the borderline cases referred to above, it is necessary to bridge the gap between a knowledge of the energy conversion in air and the energy actually communicated to the medium. For this purpose a very thin-walled chamber is used, the ionization in which gives an indication of the secondary particles (the "corpuscular emission") effective at the point.¹² The "extrapolation" chamber introduced by Failla is of this type. The procedure is to take observations

¹¹ 0.001293 g of air is the mass of 1 cm³ of air at 0°C and 760 mm of mercury pressure.

¹² Note that such a chamber gives an indication of the effect of the secondary particles on air (which is normally used in the chamber) and not on the medium. To investigate the latter, it would be necessary to fill the chamber with a gas whose effective atomic number was the same as that of the medium and to know the energy required to produce a pair of ions in the gas. Alternatively the energy absorption in the medium could be fairly closely calculated from that in air if the composition of the former is known.

with a gradually decreased spacing between the walls of the chamber, and extrapolate the results to obtain the value for a chamber of negligible width. With the very high-energy x rays that can now be produced by the betatron, studies of this kind, particularly for surface-effects (i.e., at the skin of the patient), will become increasingly important.

III NEUTRONS

The consideration of the measurement of neutron radiation follows on naturally from that of x and gamma radiation, for neutron radiation also produces ionization by an indirect means, namely, through the agency of secondary particles.

A neutron is a material particle of mass approximately unity on the atomic scale, that is, its mass is very similar to the mass of the nucleus of the hydrogen atom, the proton. But, whereas the proton has a positive unit elementary charge, the neutron has no charge at all, and so, unlike radiations consisting of charged particles, it is unable to drag electrons out of the atoms near which it passes. Thus it loses practically no energy by ionization, and will penetrate very much greater thicknesses of matter than, say, a proton of similar energy.

The interaction of the neutron is almost entirely with the nuclei of the atoms, and the commonest process is a simple collision which deflects the neutron with a reduced energy, and causes the nucleus to recoil with the balance of the original energy. The average energy-transfer in a collision is greatest when the neutron and the nucleus have equal masses, and becomes progressively less as the mass of the recoiling nucleus increases. The energy-transfer is greatest in hydrogen, when the neutron-energy is on the average reduced to about 37% at each collision.

In addition to these scattering collisions, a neutron may be captured by a nucleus and provoke nuclear disintegrations of various kinds, sometimes resulting in the production of "artificial radioactivity". The relative probability of such processes is generally small, however, until the neutron has been made very slow by repeated collisions. In the case of biological material, these nuclear disintegrations may usually be ignored in considering the energy communicated to the medium by a beam of neutrons. It may be mentioned in passing that the induced radioactivity produced in suitable substances is of help in making relative measurements of the "strength" of a neutron beam, and in discriminating between neutrons of different energy.

An immediate extension of the definition of the rontgen to include neutron radiation would not be very suitable for use in biology and therapy because, as pointed out above, the energy-conversion of the neutrons varies rapidly with the atomic type, even for "light" elements, in contrast to the energy-conversion of x or gamma radiation. In other words, air is no longer a satisfactory approximation to tissue (which contains so much hydrogen in the form of water and various organic compounds). For example, Gray & Read have calculated that when soft tissues are irradiated by fast neutrons, about 92% of the energy converted goes to the recoil protons, 5% to the recoil oxygen nuclei, 2% to the recoil carbon nuclei, and 1% to other effects, and that 1 g of average tissue would absorb seven times as much energy as 1 g of air for neutrons of particular energy about 3 million electron volts.

For reasons such as these, Gray & Read have proposed that energy-absorption in water should replace that in air for the purpose of neutron dosimetry. The unit dose is then

that quantity of neutron radiation which communicates to unit volume of water the same energy that is communicated by one röntgen of gamma radiation (that is about 94 ergs) This unit may be thought of as an "equivalent röntgen"

For the actual measurement of energy-absorption in a given medium, use may be made of Gray's Principle of Equivalence. In a hydrogenous material, the "corpuscular emission" is predominantly composed of recoil protons. The application of the method has been treated in detail by Gray. A relative measure of exposure that has been widely used in practice is the ionization produced by the neutron beam in the Victoreen type of x-ray "thimble" chamber dosimeter. This arbitrary unit is known as the "n" unit.

IV CHARGED-PARTICLE RADIATIONS

All charged particle radiations may be considered together, for they have this in common, that by virtue of their charge they ionize directly, and in a qualitatively similar manner. Such radiations include electrons (beta particles), and the whole range of swiftly moving atomic nuclei, best-known of which are the helium nuclei or alpha particles, emitted by natural radioactive substances. Of these, electrons are practically the only kind of radiation used as an external beam, and even these not widely. But with the development of the betatron for producing very intense beams of high-energy electrons, the therapeutic applications may well be extended.

Since x and gamma radiations produce their effects via the intermediary of secondary electrons, it is clear that the röntgen unit may legitimately be used for expressing dose in the case of a primary beam of electrons. A measurement of the ionization per unit volume of air gives the dose directly in röntgens¹¹. This concept is also satisfactory for any other directly-ionizing radiation. The ionization in a "thimble" chamber is now independent of the nature of the walls, provided the primary radiation is not appreciably attenuated.

¹¹ The true energy absorption for a medium of specified atomic make up could be calculated from this röntgen dose.

or reflected by them. Thus the dose rate of the primary beta radiation from "unscreened" radium plaques has been measured in röntgens.

In some cases the radioactive substances are dispersed throughout the biological material. For example, radioactive phosphorus is used therapeutically for leukaemia and biological specimens have been immersed in an aqueous solution of radon. For such cases, slightly different concepts are appropriate, for the radiation is usually absorbed completely within the medium. Thus, knowing the total quantity of radioactive substance introduced, and the total energy emitted by each disintegrating atom, the quantity of energy communicated to the medium is known, i.e. the fundamental biological quantity is known at the outset. It merely remains to compare this true energy-absorption¹² with that which is produced by other radiations in order to express it in "equivalent röntgens". This involves the adoption of some convention.

The actual energy liberated in 1 g. of the medium may be compared with the energy communicated by one röntgen of x or gamma radiation to 1 g. of air, which is a definite quantity equal to about 85 ergs, or it may be compared with the energy communicated by one röntgen of x or gamma radiation to 1 g. of the medium in question, which is not a definite quantity, but depends on the quality of the radiation and the nature of the medium. In view of the heterogeneous nature of "tissue", it is perhaps as well to base the comparison on energy-absorption in air¹. Thus, to arrive at the dose in equivalent röntgens, it is merely necessary to know the total amount of the radioactive material, the energy-emission per disintegrating atom, and the total mass through which the material is dispersed, from which is deduced the energy liberated per unit mass of the medium, which is divided by 85.

¹² Note that this energy is determined solely by the radioactive substance and is entirely independent of the medium in which the substance finds itself.

¹ The energy absorption in water (for hard gamma radiation) i.e. Gray's energy unit is in many cases a better basis for comparison. This equivalent röntgen corresponds to about 94 ergs per g.

[Note: A comprehensive bibliography of this subject would be out of place here. The following selection of references is arbitrary and in no way representative. It merely includes work referred to explicitly in the text and a few random papers which may serve as a possible entry-point into the literature.]

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TOTAL ENERGY-ABSORPTION IN RADIOTHERAPY

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The dose of radiation absorbed at a point affecting individual structures, such as chromosomes, determines the local effect on these structures, and is the effect which is desired by the radiotherapist in the neighbourhood of the malignant

any size of field, the energy absorbed at any point of the beam would be the same, at the same depth, as for the saturated pencil. Thus, assuming that all the scattered radiation is absorbed and that none escapes from the body, the volume dose is estimated by the product of the area of the field on the skin, the dosage in rontgens (corrected to allow for the "unsaturation" of the field) and a graph-reading. The graph (Fig 1) is obtained by integrating the area under the depth-dose curve for the saturated axial pencil of a very large field. The correction for unsaturation is the ratio of the dosage-rate with maximum scatter to the measured axial skin-dose of the field concerned.

Thus, comparing a field of 400 cm² and one of 50 cm² we have the following factors (200 kV, constant potential

TABLE I

No. of radiation	Type of radiation	Type of technique	Potential (kV)	Filter	Mean wavelength Å	Focal distance (cm)	Diameter of field (cm)	Gramme rontgens to 10% contour	Ergs/cm ² /r
1	x rays	Rontgen cautery	45	Unfiltered Tube only	0.90	2.0	1	71.5	36
2	x rays	Contact therapy	60	Tube only 0.2 mm Ni equiv	0.33	5.0	4	4.200	730
3	x rays	Deep therapy	200	1 mm Cu	0.12	50.0	10	96.560	3,200
4	x rays	Super voltage	400 (peak)	4 mm Cu	0.069	50.0	10	110.000	3,100
5	γ rays	1-gramme unit	—	1 mm Pt equiv	0.014	5.0	5	14.594	3.020
6	γ rays	5-gramme unit	—	1.4 mm Pt equiv	0.013	8.2	8	51.587	3,060

[From Mayneord (1940)]

tumour. To enhance this effect by variations in quality, dose, dosage-rate, fractionation, and total time, is one of the chief aims of the radiotherapist. At the same time, however, general effects are produced by the radiation and manifest themselves in organs which have not been irradiated. These effects are troublesome and difficult to avoid and, in attempting to correlate them with dose, I perceived the necessity for estimates of the total energy-absorption by the body. I therefore asked Dr Haphey to investigate the problem so as to provide an estimate of the volume-dose in "rontgen cubic centimetres" (r cm³). Mayneord, however, was also engaged in a similar investigation on different lines, and had coined the terms "integral dose" and "mega-gramme-rontgen". The latter is a more convenient unit and a more euphonious term, and so is to be preferred to the term "rontgen cubic centimetre". It is intended in this short paper to discuss briefly the physical approaches, attempts at correlation with biological effects, and then the practical value of the conception of volume-dose.

Physical Estimates

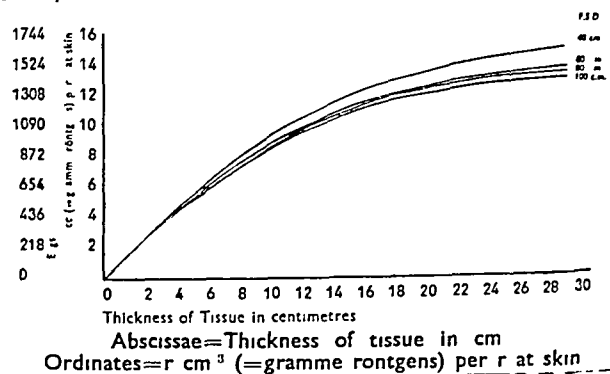
Haphey (1940, 1941) points out that the energy absorbed in the axial pencil of a very large field is maximal because the proportion of scatter is maximal. If all the radiation scattered outside the geometrical beam were confined to it then, for

1 mm Cu 1 mm Al 40 cm FSD)¹

Field size (cm ²)	Dose rate (r/min)	Tissue thickness (cm)	Graph reading	Volume dose per rontgen at skin
400	92	20	13	13 × 400 × $\frac{1}{13}$
50	76	20	13	13 × 50 × $\frac{1}{13}$

Mayneord approached the problem on different lines, and has done a great deal of work alone, and with his collaborators, on the theoretical and practical aspects of the problem.

FIG 1 GRAPH RELATING VOLUME DOSE PER RÖNTGEN AT SKIN SURFACE TO THICKNESS OF TISSUE THROUGH WHICH THE BEAM PASSES (From Ellis 1945)



¹[FSD] Focus skin distance — Ed.]

His original paper (1940) described a method of integrating the dose by measuring the volume of rotation between the isodose surfaces of a beam by practical measurement of the moment of the area, and gives values for volume-doses of different types of radiation which throw into sharp contrast their differences in this respect (See Table I)

He discusses (1944) the mathematical theory of volume-dose and derives the following interesting generalizations. For a beam in which the dose-contours in a given plane-section are straight lines perpendicular to the axis of the beam, and the dose falls linearly with depth, the integral dose is given by the product of the mass of the body concerned and the dose at its centre of gravity. From investigations made in collaboration with Clarkson (Mayneord & Clarkson, 1944) on a wax model of a man, tables were constructed giving the "average" dose throughout a patient of a given thickness and a given quality of beam. (A body of mass M receives an average or mean dose \bar{D} when the Integral or Volume Dose $\Sigma = \bar{D} M$). This "average dose", corrected for focus skin distance and multiplied by the mass of the patient gives the "integral dose".

Mayneord further (1945) discusses the mathematical theory of integral dose in radium-therapy. It appears that, for concentric shells about a radium source, the volume-dose of each shell is proportional to its thickness and the number of milligramme-hours (mgh) at the centre. Moreover, there is a reciprocal relationship between the source emitting radiation and the volume receiving it. "The integral dose throughout any volume whatever due to a finite source, uniformly filled with radioactive material, is equal to the integral dose throughout the original source if the 'receiver' be filled with radiating material of the same uniform density." A graph is given from which the integral dose per mgh for point-sources near the centre of an absorbing mass, may be read (Fig 2). For a sphere of radius a , the volume-dose throughout the sphere was calculated by Mayneord to be

$$\Sigma = 8.3 \times 4 - a \times F \text{ per mgh}$$

$$\text{where } F = 2a + \frac{a^2 - c^2}{c} \log_e \frac{a+c}{a-c}$$

c being the distance of the point-source of radium from the centre of the sphere, and the relationship of F to c/a is given in Fig 3, taken from Mayneord. Examples of volume-doses are given for certain situations and techniques met with in practical radium therapy.

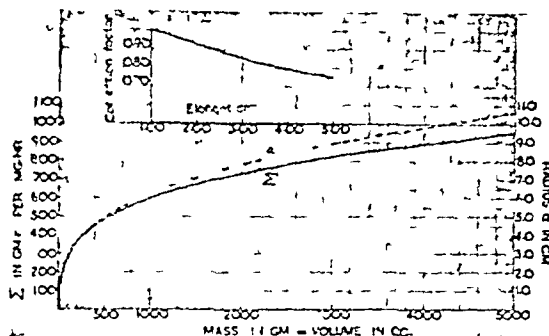
For example

- i In treating a carcinoma of the maxillary antrum with a dose of 3,000 mgh, the volume-dose is assumed to be that for a sphere of radius 9.8 cm and of mass approximately 4 kg with the radium relatively centrally placed.
 $\Sigma = 3,000 \times 0.89 = 2.7$ megagramme-rontgens, 0.89 being the graph reading (see Fig 2)
- ii In treating carcinoma of the cervix uteri with a dose of 6,000 mgh, the integral dose is calculated as about 9.8 megagramme-rontgens, neglecting the absorption by the filters in which the radium is packed

Measurements of Volume-dose

Measurements of volume-dose have been attempted by Boag (1945), using the model constructed by Grimm

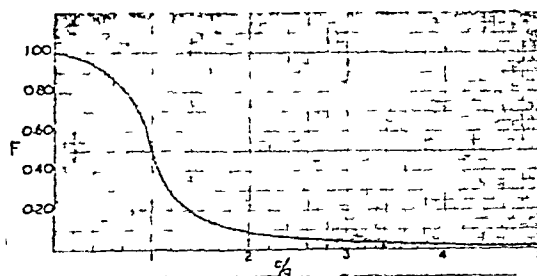
FIG 2



Integral dose per mgh for point-sources near the centre of an absorbing mass of known volume and mass (From Mayneord 1945)

(1939, 1942). This model consists of spaced plates 6 mm thick, of density 0.985, graphited and spaced 2 mm apart by

FIG 3



Curve relating

$$F = 2a + \frac{a^2 - c^2}{c} \log_e \frac{a+c}{a-c}$$

to $\frac{c}{a}$ where C is the distance of a point source of radium from the centre of a sphere of radius a (From Mayneord 1945)

thick washers of the same material (cellulose acetate) as the plates. Alternate plates are connected together, thus forming

FIG 4



Grimm's ionization chamber man in position for treatment to the head (From Boag 1945)

two groups of plates, each of which is connected to opposite poles of a battery with a sensitive galvanometer in circuit, to measure the total ionization current collected from all the air-gaps (i.e., from the whole body) under radiotherapeutic conditions. Under these conditions guard-rings were found to be necessary to prevent insulation-leakage, and allowance had to be made for their effect. Moreover, the absorption-conditions for a wide range of wavelengths and various angles of incidence of the x-ray beam had to be similar to those for the human body. These points were all dealt with, and curves were constructed from which volume-doses delivered with x rays of HVL 2-4 mm Cu can be estimated quickly and fairly accurately.² Boag's measurements indicate that the volume-dose depends principally upon the area and site of the field. The FSD linear dimensions of the patient and HVL of the beam have much less effect.

Photographs of the model are shown in Fig 4 and 5, and curves representing some results in Fig 6 and 7 from Boag (1945).

Mayneord & Clarkson (1944) also constructed a wax model for making measurements to estimate the volume-dose when the whole body is irradiated. The actual measurements were made in slabs filled with the suggested powder mixture of Spiers (1943), and estimated both by the average-dose method

FIG 5



Photograph showing the general appearance and method of construction of the trunk of Grimmett's ionization chamber "man". (From Boag 1945)

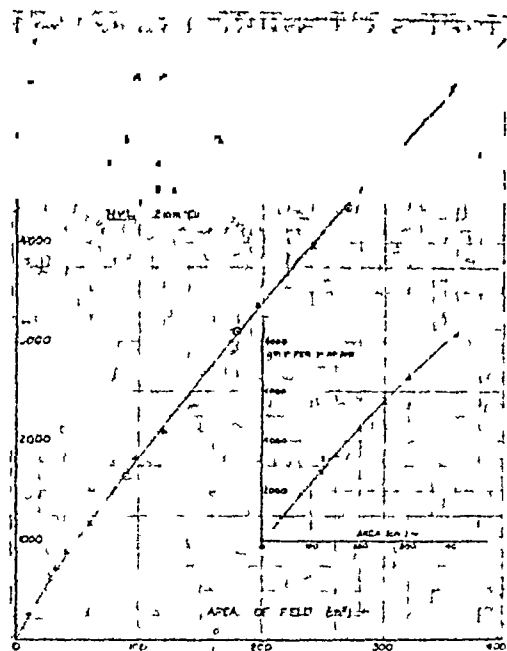
and by planimeter measurements of the areas between isodose curves in the body-section (Fig 8). Their results are represented graphically in Fig 9 and 10, which show the volume-dose in gramme-rontgens per rontgen to the surface of the body (70 kg) for various half-value layers. It is seen that there is a rapid rise up to HVL = 0.2 mm Cu (= about 100 kV with 0.15 mm Cu filter) followed by a less rapid change.

Value of the Conception of Volume-dose in Radiotherapy

The volume-dose might conceivably help in deciding on modifications of technique, and might help in correlating physical dose with general effects of radiation.

It must be realized, however, that the physical methods

FIG. 6



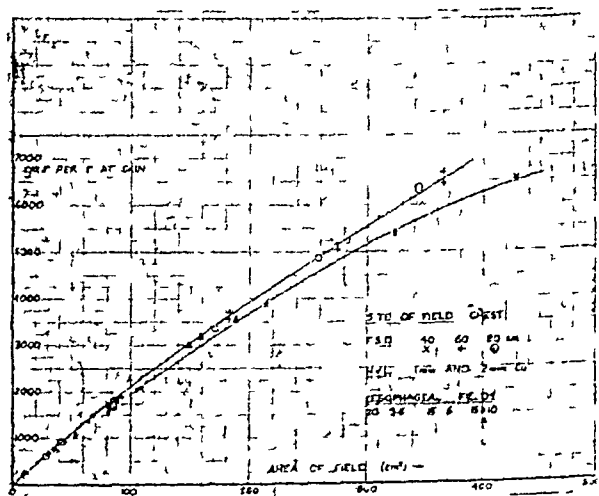
Relation of volume dose to field area for irradiation of the pelvis. Inset curve shows relation for roentgen dose measured without scatter, which is linear up to 200 cm². (From Boag 1945)

hitherto described for estimating volume-dose suffer from certain inaccuracies. The chief of these are due to the fact that allowance is not made, in the physical methods, for the variable tissues and their densities in the human body, while biologically one cannot expect uniform behaviour of various tissues for a given physical dose.

Physical Factors

The author has attempted elsewhere to show the effects of certain physical factors on volume-dose (1942, 1945).

FIG 7



Relation of volume dose to field area for chest irradiation. The lower curve is for the shorter FSD (40 cm). (From Boag 1945)

² [Half value layer. See footnote on p. 51.—Ed.]

TABLE II EFFECT ON VOLUME DOSE OF INCREASED FSD (CARCINOMA OF OESOPHAGUS, 40 cm FSD AND 100 cm FSD)

200 kV 1.5 mm Cu HVL Field size 15 × 4 cm ²		Tumour-dose = 6 000 r Eight fields	
FSD = 40 cm Field-dose = 3 400 r		FSD = 100 cm Field-dose = 2 800 r	
r cm ³ /cm ² /r	Field thickness (cm)	r cm ³ /cm ² /r	
13.4	1	11.79	
13.4	1	11.79	
13.82	2	12.47	
13.82	2	12.47	
13.82	2	12.47	
13.82	2	12.47	
15.3	3	13.6	
15.3	3	13.6	
112.68		100.66	
TOTAL ENERGY-ABSORPTION			
$3\,400 \times 60 \times 126 \times \frac{92}{76.3} \text{ r cm}^3$ $= 3.11 \times 10^7 \text{ r cm}^3$ (125%)		$2\,800 \times 60 \times 101 \times \frac{92}{76.3} \text{ r cm}^3$ $= 2.05 \times 10^7 \text{ r cm}^3$ (100%)	

Field-Area

The volume-dose is almost proportional to the field-area

Focus-Skin Distance

A comparison is made in Table II of the volume-dose using two techniques for treating carcinoma of the oesophagus the only difference between them for a given tumour-dose being the difference in FSD. These estimates are based on Hapley's method (1941) and it should be pointed out that Boag's graph (Fig 7), for a similar technique, shows no appreciable difference with the two FSD and gives a rather higher value (36 megagramme-rontgens) than either of the two techniques compared above.

Quality of the Beam

The effect of the quality of the beam as determined for whole-body radiation has been mentioned already (see Fig 9, 10). Also Phillips (1942) demonstrated that for a given tumour-dose there is a considerable difference in volume-dose between techniques using 200 kV and 1,000 kV (see Table III).

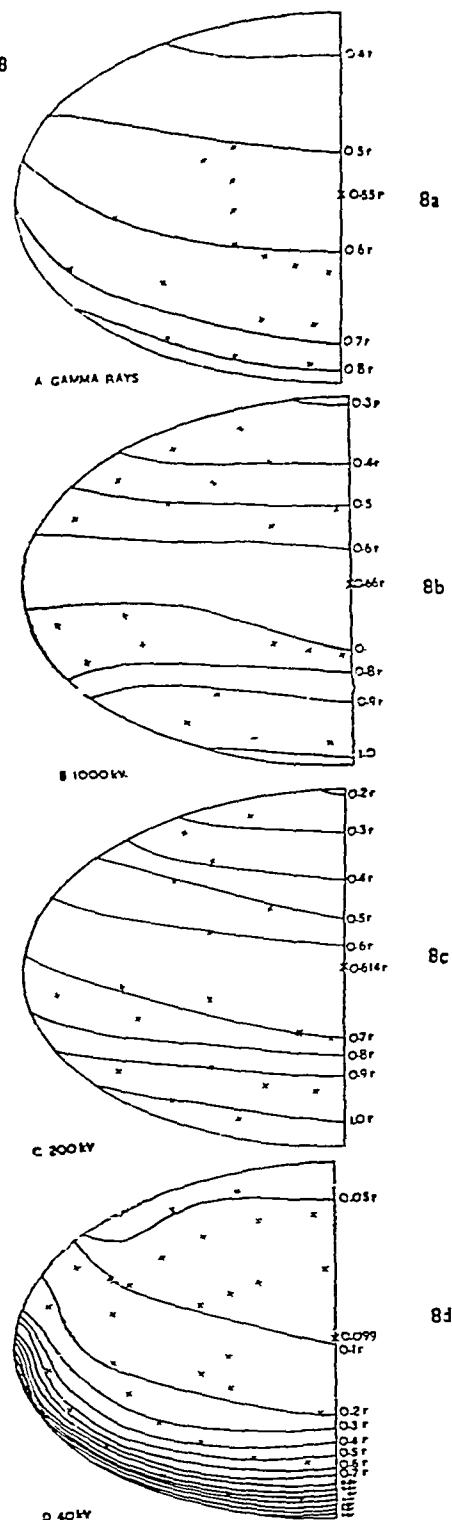
TABLE III

200 kV	For a tumour dose of 6 000 r	1 000 kV
2 400 r	Dose per field	1 620 r
5 030 r	Max skin dose	3 400 r
67	Volume-dose (Megagramme-r)	41

The Arrangement and Number of Fields

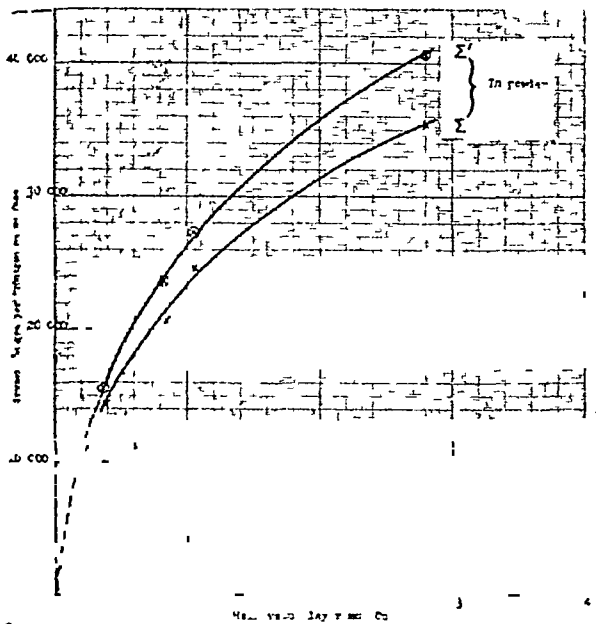
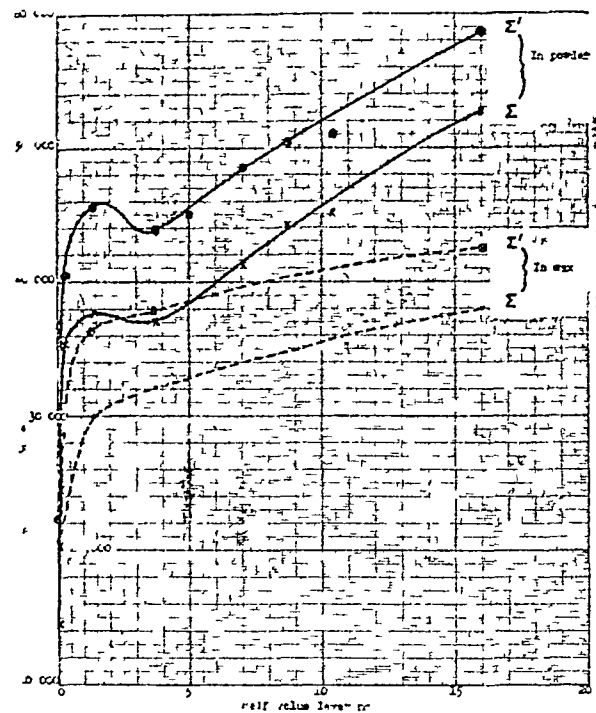
The author has discussed (1945) the effect of these factors for two sets of conditions

FIG 8



Shows isodose distributions in a cross-section of the trunk for various qualities of radiation (From Mayneord & Clarkson 1944)

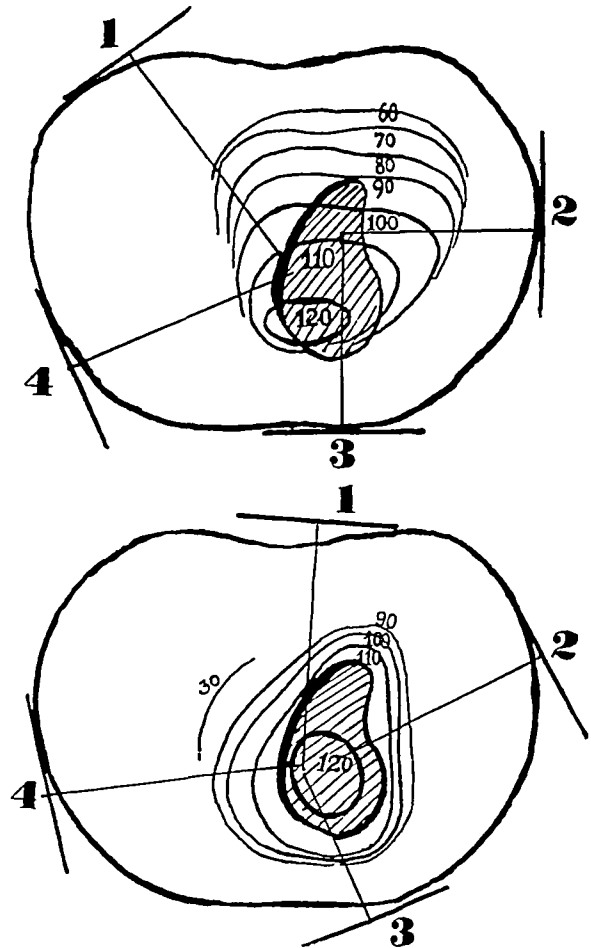
FIG 9 and 10



Comparison of the values of integral dose obtained in a model patient constructed wholly of wax and in a model constructed of Spiers' mixture for various radiation qualities (From Mayneord & Clarkson 1944)

a Using Ungar's (1943) conception of the economy-quotient, it can be shown that the greater the homogeneity of dosage, the smaller the volume-dose. Ungar gives examples of arrangements of fields for treating a case of carcinoma of the cervix in relation to the "economy quotient" and the volume-dose. The economy-quotient

FIG 11



TOP
 $D'_{\text{max}} = 120\%$
 $D'_{\text{min}} = 110\%$
 $D'_{\text{max}} - D'_{\text{min}} = 30\%$ (heterogeneity factor)
 $\frac{D'_{\text{max}} - D'_{\text{min}}}{\text{Het Factor}} = \frac{90}{30} = 3$, the economy quotient

BOTTOM
 $D'_{\text{max}} = 120\%$
 $D'_{\text{min}} = 110\%$
 $\text{Economy quotient} = \frac{110}{10} = 11$
 $\text{Volume dose} = 4.36 \text{ megagramme-r}$
 (From Ellis, 1945)

is the ratio of the minimum tumour-dose to the difference between the maximum and minimum tumour-doses, and is a measure of the efficiency of the technique. It seems that, other things being equal, the arrangement which gives the greater economy-quotient gives the smaller volume-dose. Since the economy-quotient is highest when the difference between the maximum and minimum tumour-doses is smallest, it follows that the greater the homogeneity, the smaller the volume-dose (see Fig 11).

b Using two wedge-fields as described by Ellis & Miller (1944) (see Fig 12), the volume-dose, for 1,000 r tumour-dose

calculated by me from measurements made by Boag, is 1.42 megagramme-röntgens. An appropriate technique to achieve the same treatment without wedge-fields would be to use 2 lateral 10×8 cm² fields and one 6×4 cm², e.g., to the skull. Under these conditions, the volume-dose for 1,000 r tumour-dose is 2.4 megagramme-röntgens—obviously higher than that for the wedge-fields.

Volume-dose and Tolerance-dose

Mayneord & Clarkson (1944) by their work on whole-body irradiation have put the energy-absorption by the body under such conditions in true perspective, and a new aspect of the conception "tolerance-dose" has emerged. For whole-body irradiation, the volume-dose relationships for 40 kV, 200 kV and gamma radiation respectively are in the ratio of 15:35:40, for a wide beam enclosing the body, and a very large FSD—i.e., the conditions under which radiation is received by medical workers. In other words, for a given dose in "röntgens" to the skin—which is the present method of estimating tolerance-dose—the energy absorbed by the body may vary considerably from one type of radiation to another. Since the biological effect considered in the internationally accepted figure of 10^{-1} r/sec is a general effect rather than a local one, it would seem more accurate to aim at a volume-dose estimation rather than a surface-dose. It is interesting to note that the international figure for diagnostic x rays (10^{-6} r/sec) is three times that for gamma rays, and that this ratio, decided by experience, is of the order of the ratio of the volume-doses of 40 kV x rays and gamma rays.

The following Table (IV) shows the influence of technique on the volume-dose in treating cancer of various sites.

The discrimination now possible between volume-dose and surface-dose should permit of new standards. That limiting the permissible general radiation should be a volume-dose, and that limiting the local radiation a surface-dose, which

TABLE IV. TECHNIQUE AND TOTAL ABSORPTION OR VOLUME-DOSE HVL-0.15 mm Cu FSD-40 cm

Region	Dose 1,000 r	Fields No. cm ²	Total absorption r cm ²
Tonsil	4.5	$2 \times 10/8$ $2 \times 6/4$	7.77×10^6 —
Fauces	4.0	$2 \times 10/15$ $2 \times 6/4$	11.26×10^6 —
Larynx	5.0	$2 \times 6/8$ $1 \times 6/4$	— 4.53×10^6
Brain	4.0	$2 \times 10/8$ $1 \times 6/8$	— 11.97×10^6
Bladder	5.6	$8 \times 8/10$	17.24×10^6
Pelvis (supplement to radium)	3.0 3.0	$2 \times 10/15$ $2 \times 10/15$	25.97×10^6 —
Oesophagus	6.0	$8 \times 15/4$	31.1×10^6
Lung	4.0	$4 \times 10/15$	30.3×10^6
Lung	5.5	$5 \times 6/8$	19×10^6

might presumably be higher than the figure used hitherto, which, in effect, has no real value for those working with radium.

Correlation of Biological Effects with Volume-dose

The ultimate practical value of the conception of volume-dose will depend on the possibility of using it as a criterion for modifying technique, and as a means of obtaining more

FIG 12

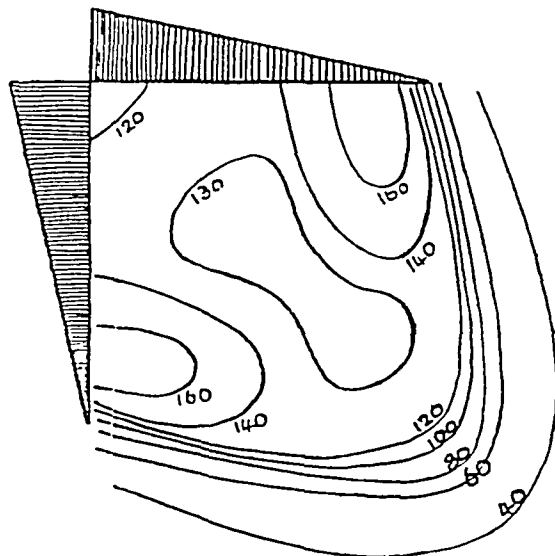
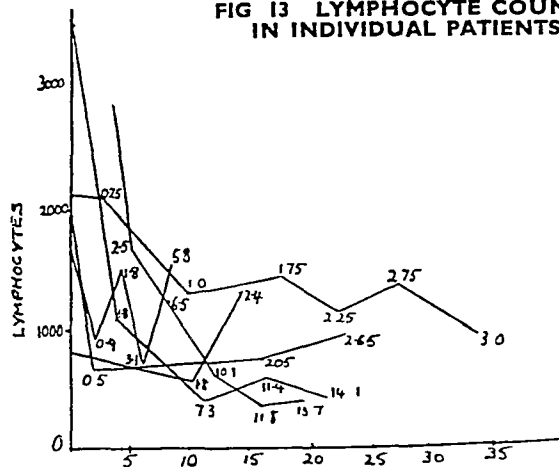


Diagram of the isodose distributions produced by combining two x-ray beams at right angles using wedge filters (From Ellis & Miller 1944)

knowledge of the action of radiation. The physical factors hitherto discussed indicate the manner of influencing volume-dose by technical variations.

Modification of technique will be considered by a radio-therapist only if the general effect of the radiation is of such magnitude as to interfere with the delivery of a local dose.

FIG 13 LYMPHOCYTE COUNTS IN INDIVIDUAL PATIENTS



Abscissae = days after commencement of radiation. The volume-doses received are indicated on the curves. Note that although the trend is marked, each curve shows a rise at some time during treatment (From Ellis 1945)

General effects, as distinct from local effects, however, might be due to the local effects of radiation. Thus, the local effect of radiation on the mouth and oesophagus might have a profound effect indirectly on the general nutrition, the lighting-up of local infection might also have a marked general effect, while local oedema in such specialized structures as the lung and brain might have a marked effect on general well-being. Moreover, the variable structure of the human body makes estimates of the usual accuracy demanded in physics almost impossible. In addition, different regions of the body differ in sensitivity, while the variation from one human being to another, due to metabolic, physical and psychological differences, conspires, with the influences mentioned above, to make difficult the correlation of biological phenomena with volume-dose. Nevertheless, some attempts have been made.

The Volume-Dose Limiting Radiation Technique

In Table IV the volume-dose for lung and oesophagus of about 30 megagramme-rontgens in one month is near the limit of what the patient can tolerate. Levitt (1938), in an account of trunk-bath radiation, finds that the maximum dose to the surface which can be tolerated is 1,500 r (measured with backscatter), though treatment under such conditions has not to be stopped because of local effects, e.g., on skin. This corresponds to a volume-dose of about 30 megagramme-rontgens in 6 weeks. Phillips (1942) found that 40 megagramme-rontgens was less than the maximum dose that could be tolerated in about 4 weeks in treating a rectum. At the London hospital I find that treatment to the whole abdomen permits of a volume-dose of about 40 megagramme-rontgens in 3 weeks, so that it appears that a patient will tolerate a large volume-dose to a smaller part of the body more readily than to a large part.

Apart from therapeutic conditions such as these, it does not seem from Table IV that the volume-dose is likely to limit technique as at present developed. It is possible to imagine conditions, however, under which such limitation might occur. Suppose, for instance, that instead of being delivered in one month, a volume-dose of 7 or 8 megagramme-rontgens is to be given to a patient in treating a tongue in one day. It might be that, under such conditions, volume-dose is a limiting factor. Such a possibility is not inconceivable in the light of the hypothesis suggested by Gray (1944) that the number of fractions rather than the total time is more important. If this is true, then techniques might be developed necessitating the administration of very large doses in many fractions in a very short time.

What Biological Phenomena can be Correlated with Volume-dose?

The phenomena must be general, as distinct from local, and may be subjective or objective.

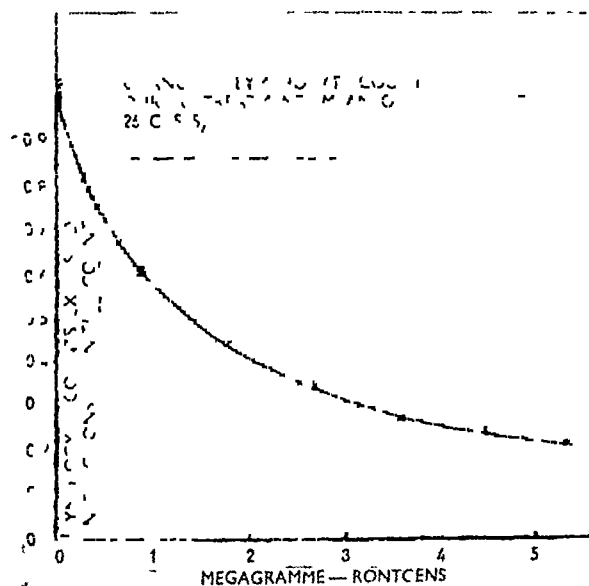
Subjective phenomena such as malaise, nausea, vomiting, and headache are very difficult to correlate, especially since so many of these symptoms might be produced by general upsets not due to radiation.

Objective phenomena may be measurable or not. Here we shall consider measurable phenomena only. They may be divided into (a) blood-counts, (b) other measurements.

Blood-counts are the easiest tangible evidence to obtain of the effects of radiation.

Ellis (1942) tried to correlate the blood-counts, corpuscular volume, and other factors, with volume-dose. No correlation was possible. Fig 13 shows types of lymphocyte-count obtained. Although there is an average trend, individual counts behaved very differently, even rising during relatively rapid administration of radiation at some part of every

FIG 14



Curve of average lymphocyte counts of 26 patients all treated by a similar technique related to volume dose in megagramme r (From Bush 1943)

curve. Other types of cell are much more erratic. Thus correlation in individual cases is impossible. From the work of Bush, however, there appears almost a mathematical correlation. Fig 14 is based on average lymphocyte-counts of 26 cases treated for carcinoma of the mouth, pharynx and larynx. The possibility of individual variations as in Fig 13 still, of course, exists. Experience of abdominal-bath treatments provides the same type of curves as in Fig 13. Thus the volume-dose cannot be correlated with the lymphocyte-count (and still less with other cell-counts) in individual cases.

The effect of x rays on the blood-concentration of ascorbic acid in animals and patients has been investigated by

TABLE V

Diagnosis	Treatment (200 kV) (tumour dose)	Ascorbic acid mg % in plasma	
		Before	Immediately after
Breast carcinoma	Post-operational x ray 300 r	0.501	0.435
Breast carcinoma	Post-operational x ray 300 r	0.836	0.794
Mediastinal tumour	x ray 350 r	0.303	0.286
Breast carcinoma	Pre-operational x ray 1,200 r	0.420	0.336

Kretschmar, working with the author (Ellis, 1945) There is no doubt that x-ray treatment reduces the ascorbic-acid content of the blood and of the tissues in animals, and the ascorbic-acid content of the blood in patients Table V shows a diminution of the plasma ascorbic acid during treatment in three breast cases and a case of mediastinal tumour

The technical arrangements for the breast cases are similar in all three patients, and it is obvious, on a superficial examination of the figures, that there is a qualitative but not a quantitative correlation with volume-dose even in these few cases

It seems likely that the chemical changes which occur in

the body soon modify any substances which might be formed, so that it might be impossible even to achieve biological correlation, although the most hopeful line of attack on the problem would be to try to estimate breakdown-products, such as adenosine, as being the possible initial substances Other effects seem likely to be secondary, whether chemical, cytological or physiological, and as such will not offer any real correlation

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ON TECHNICAL METHODS IN X-RAY THERAPY

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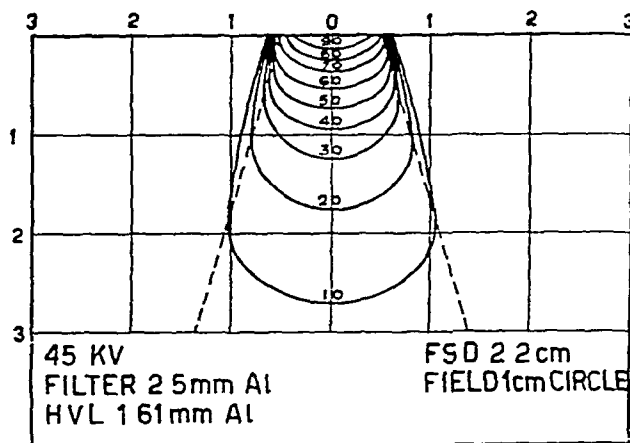
General Survey

X-ray therapy is often roughly divided into various classes—contact therapy, superficial x-ray therapy, deep x-ray therapy, supervoltage therapy—yet these classes, and the various methods within each, all have certain physical principles in common Firstly, it is desired to produce a chosen distribution of x-ray dose through a patient's tissues by combining the necessary number and arrangement of fields It may be considered adequate to produce more than a certain minimum dose throughout a region, such as a tumour, with as little as possible elsewhere, without caring what the maximum in this region may be A more stringent requirement is that the dose be uniform throughout the region Ungar (1943a) has shown that under certain conditions the total radiation absorbed by the body is a minimum, for a given tumour-dose, when that dose is uniform throughout the tumour A general requirement is that the dose at the skin, where each beam enters, shall not exceed a certain value, account being taken of all contributions from other beams There may also be other regions where it is particularly necessary to keep the dose small

Secondly, it is desired to keep the radiation dose absorbed by all the healthy tissues as small as possible in relation to that absorbed in the treated volume This requirement not

only influences the manner in which the x-ray fields are arranged to give the desired dose-distribution, it also largely determines the class of therapy chosen If a lesion is near the surface of the body, or accessible through a body cavity, or with the aid of surgery, it is generally better to use a beam of less penetration and small focus-skin distance, so that the dose in the healthy tissues beyond the lesion diminishes rapidly with the depth in the tissues A rough measure of this total body-dose is obtained by summing the product of dose and volume throughout the body, though it is evident that this is only a rough guide, as the susceptibility to radiation of each element of volume as well as the dose there determines the aggregate effect (Ellis, 1946)

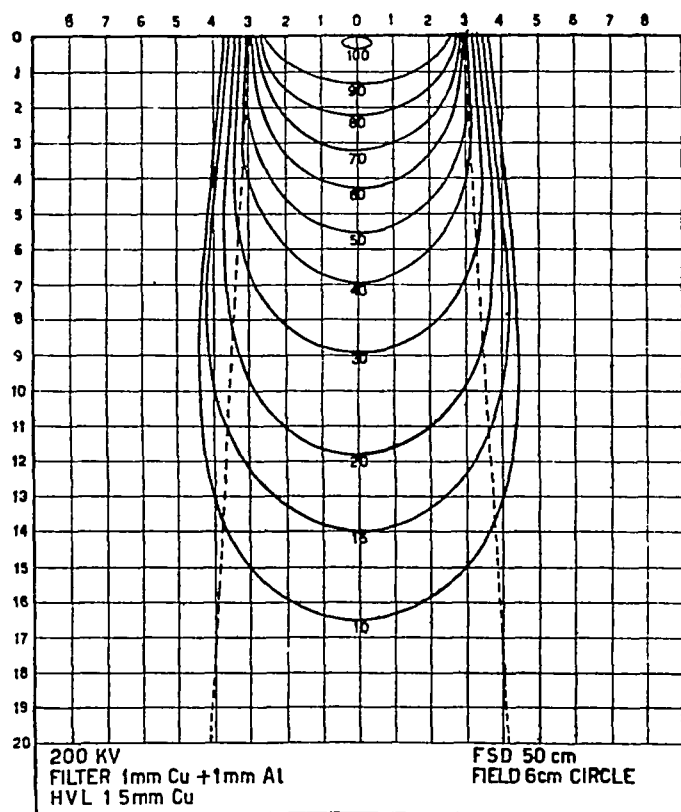
FIG 1a. ISODOSE CURVES FOR A CONTACT-THERAPY FIELD



Field 1 cm circle, focus skin distance 22 cm radiation generated by 45 kV and filtered by 2.5 mm aluminium HVL 1.6 mm aluminium (Mayneord 1943a)

The possible ways of combining x-ray fields to produce a desired distribution are studied with the aid of isodose charts. Typical charts are shown in Fig 1a (for a low-voltage contact-therapy tube), and Fig 1b (for a deep-therapy tube) (Mayneord, 1943a). The dose-distribution in a plane through the body due to a certain field is described by curves, which each join points of the same dose-rate expressed as percentages of that at the centre point of the field on the skin. Strictly speaking, these charts are not

FIG 1b ISODOSE CURVES FOR A DEEP-THERAPY FIELD



Field 6 cm circle, focus-skin distance 50 cm, radiation generated by 200 kV and filtered by 1 mm copper and 1 mm aluminium, HVL 1.5 mm copper (Mayneord 1943a)

obtained by measurements in the human body, but in a "phantom" constructed of material the absorption and scattering of x rays of which approximate to that of tissues. Generally water is chosen, but sometimes wax, mixtures such as rice-flour and sodium bicarbonate, and "pressedwood"—compressed wood-pulp boards—are used. Also, for the sake of standard conditions, the measurements are made in a phantom large enough to approximate to a semi-infinite slab. Deviations from these charts which are likely to occur in practice, due to the nature of the human body, are considered later.

When a suitable distribution of fields has been chosen to give a desired dose-distribution on paper, means must be found to direct the x-ray beams sufficiently accurately to

give this distribution in practice. If the absorption of the radiation in the healthy tissues is to be a minimum, beams no wider than necessary must be used. This makes accurate aiming very important. Rarely is more than one tube used at a time, usually a single tube is directed successively in the desired ways. This may be done by adjustment of the tube-applicator to skin-markings, with orientation of the tube to calculated angles. To assist in this, numerous beam direction devices have been developed. Alternatively, jigs can be made, which are attached to the patient in fixed positions, and aid in the correct adjustment of the tube. Finally methods must be mentioned in which there is a relative rotation of x-ray tube and patient, so that the axis of rotation and the x-ray beam pass through the tumour roughly at right-angles to each other.

The desirability of beams being no wider than necessary was mentioned earlier. A broad beam provides a greater depth-dose than a narrow beam, as the dose is enhanced by the scattering from a greater block of tissue. Beams broader than the tumour cross-section have been used to give an adequate tumour-dose at a depth, but it is preferable to use more beams with a cross-fire technique, or use a more penetrating radiation, so that the minimum beam-width will suffice.

Illustrative Dose-distributions

a Single fields These are suitable for treatments where the maximum dose must be given to the surface. In this case it is desirable that the dose-rate should decline rapidly, and an easily absorbed x-ray quality, i.e., one generated by a relatively small kilovoltage, is therefore chosen—the so-called Chaoul or contact therapy. Meredith (1940, 1945) has shown that the dose received by the first millimetre or so of tissue is appreciably altered by secondary radiation from the applicator and metal parts in the tube, and can be reduced in relation to the dose at 5 mm depth by spraying the applicator with aluminium paint and covering the tube window with aluminium foil.

b Multiple fields When it is desired to produce a relatively uniform dose-distribution through a volume, or to dose a tumour at a depth to a greater degree than the skin at the area of entry of the x rays, it is evident that a number of beams must be used which all include the tumour, but enter through different skin areas. The simplest case is that of two oppositely-directed beams. This is useful in the treatment of the lip, eyelid, or nose, by contact therapy, and gives a fairly uniform dose-distribution (Flood & Smithers, 1939). It has been discussed by Smithers (Honeyburne, Lamerton, Smithers & Mayneord, 1939) and by Wilson (1943a). With the usual deep-therapy conditions—40 to 100 cm FSD (focus-skin distance), about 1 mm copper HVL (half value layer)¹—a dose varying between 90% and 105% of the skin dose (the sum of contributions from both fields) can be obtained through a thickness of about 12 cm, i.e., the diameter of the average neck.

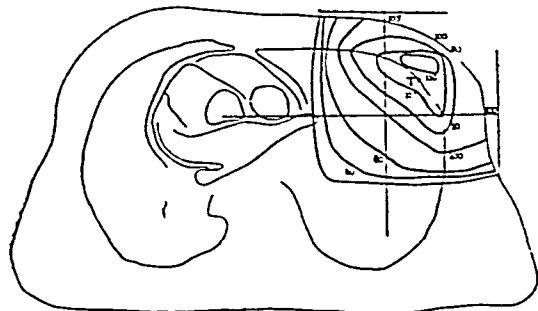
Two fields at right-angles give a region of maximum dose on the bisector, and nearer to the apex of the angle than the point of intersection of their axes. Wilson (1942a) has shown

¹ See footnote on p. 51—Ed.]

that this can be put to advantage, for example in the treatment of a tumour of the lung, situated near the anterior chest wall (Fig 2)

Skill in arrangement of multiple beams is acquired by a study of existing dose-distributions, of model isodose surfaces (Mayneord, 1943b), and by trial arrangement of isodose charts and modifications of these arrangements. A few examples are given below. When the beam axes are co-planar,

FIG 2. FIELDS PRE ARRANGED USING DOSE CONTOURS



Tumour uniformly irradiated with maximum dose equal to 120% of maximum skin dose. 2 10 x 8 cm fields only. Irradiation of a tumour of the lung near the anterior chest wall by two fields at right angles. The maximum dose occurs on the bisector of the angle between the fields, but nearer to the apex of the angle than the point of intersection of the axes of the two beams. The fields are arranged to give this region of maximum dose at the site of the tumour (Wilson 1942a)

the case is simpler. Wilson (1942a) has shown an arrangement of three fields to give a good dose-distribution for treatment of a larynx (Fig 3). A case in which it is desired to keep the x-ray dose low over a region is in the treatment of the cervix uteri by combined x ray and radium. Intra-uterine and vaginal radium applicators, which give an adequate local dose, give too little to the more distant parts of the pelvis, which must therefore be dealt with by x rays. The beams are directed to give maximum effect at the lateral wall of the pelvis, but be limited where the gamma rays are effective, the two together giving a uniform distribution. Reference should be made to papers by Walker (1940), and Sandler (1943) for diagrams which give the dose-distribution throughout the pelvis.

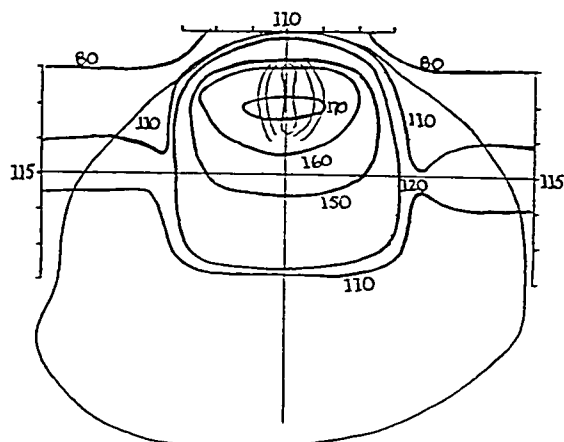
More complicated cases of summation of three and of four beams, whose axes are not co-planar, have been given by Lamerton and Mayneord (Honeyburne, Lamerton, Smithers & Mayneord, 1939) and by Ungar (1945) respectively. Ungar develops methods of treating vertebrae with 200 kV radiation which give a dose at the lesion about 1.4 times as great as that at any skin area, except for certain small field-overlaps not exceeding 5 cm².

The method of rotating the patient (or tube) carries the multiple-beam technique to the limit, where the skin area of entry of the beam becomes a continuous belt round the patient. Nielsen (1945) has described the application of this method in the treatment of cancer of the oesophagus. The patient sits on a stool which rotates him once in about 15 minutes about an axis along the oesophagus, which is 50 cm from the tube-focus. A narrow beam is used, and to ensure that it includes the oesophagus the shadow pattern of this

beam is viewed on a fluorescent screen. With radiation of 0.9 mm copper HVL the skin dose on the anterior and posterior surfaces is 40%-50%, and in the axillae 25%-35% of the central dose. The longer radius from the axis of rotation to the axilla gives the skin in this region a greater linear velocity, so that it more quickly crosses the x-ray beam. Jensen (1945) has described irradiation of the pelvis with a tube which rotates through 180° about an axis in the supine (and then prone) patient. Various modifications are possible in these methods—the shutter can be closed during part of the rotation, the angular velocity can be varied at different parts of the arc, and by tilting the beam-axis at an angle to the axis of rotation, first in one direction and then in the other, the tumour can be irradiated through two zones of skin to provide a still greater ratio of tumour-to-skin-dose. In the last case, however, the position of the maximum dose may be shifted along the axis of rotation away from the point of intersection of the beam-axis.

c Wedge fields Ellis & Miller (1944) have shown that an x-ray beam can be so modified by a wedge-shaped filter that two such fields at right-angles, with the thick edges of the wedges contiguous, give a fairly uniform dose-distribution through the block of tissue of which the two fields are adjacent sides. The dose declines rapidly outside this block. The single field with the wedge-filter, and the two fields added at right angles, are shown in Fig 4a and 4b. To produce a field like 4a the wedge must cause a very considerable absorption, so that the useful dose rate is seriously diminished. However, if adequate dose-rate is available, the arrangement is very convenient for the irradiation of lesions situated a few centimetres deep to the skin, and is specially suitable to use with a jig to give accurate direction of the beams.

FIG 3. FIELDS PRE ARRANGED USING DOSE CONTOURS

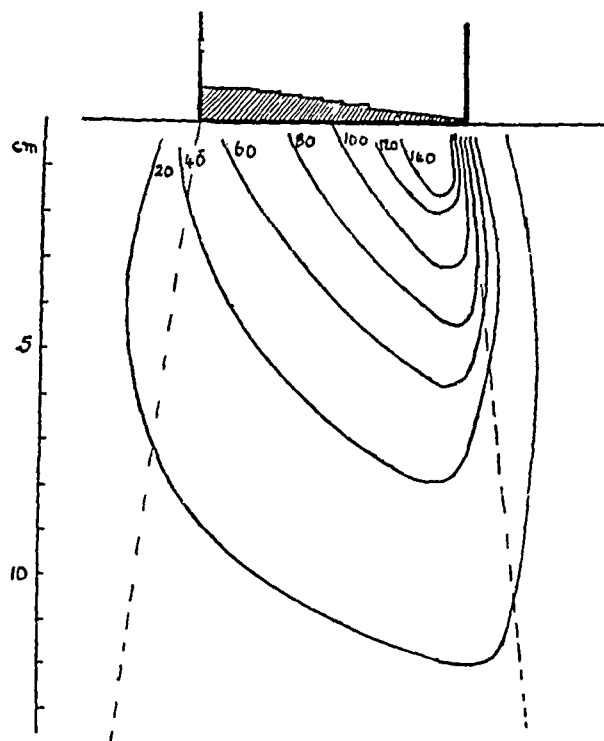


Larynx uniformly irradiated with a dose equal to 140% of maximum skin dose

Arrangement of three fields with co-planar axes to give a relatively uniform dose-distribution through the larynx 1.4 times that of the maximum skin dose (Wilson 1942a)

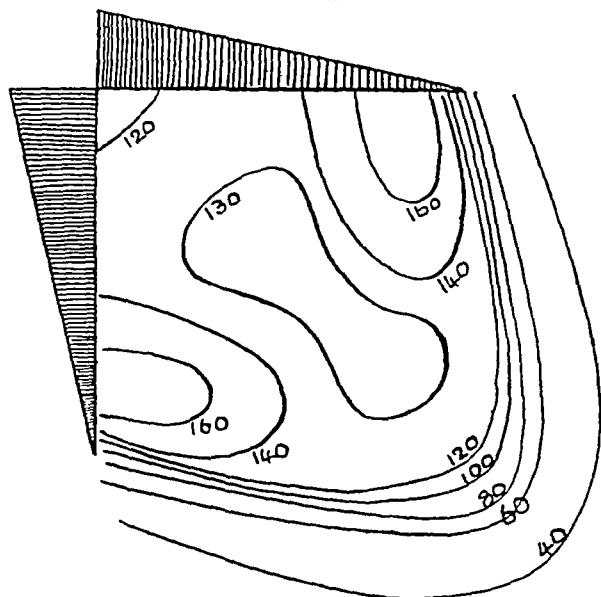
When a number of fields are chosen to give a uniform dose-distribution a complete set should be administered to a patient at one treatment, and not at intervals of a day or so

FIG 4a



Isodose curves as modified by a brass wedge-filter of maximum thickness 6.3 mm. Field 8 x 8 cm, focus skin distance HVL of the radiation 1.5 mm copper
(Ellis & Miller 1944)

FIG 4b



Dose-distribution of two fields of type illustrated in Fig 4a, arranged at right-angles, the positions of the thick edge of the wedge being contiguous. The distribution is fairly uniform through the block of tissue enclosed by the fields and declines rapidly outside
(Ellis & Miller 1944)

Methods of Study of the Dose-distribution from a Number of X-ray Beams

Most x-ray treatments require for their study the summation of the dose-distributions of several beams. If the axes of these beams are co-planar, the distribution in that plane can be found by superimposing, in the correct relative positions, isodose charts drawn on transparent sheets, and summing them in succession at the points of intersection of the curves. A convenient method is that of Ungar (1943b), who cut blue-base film (discarded diagnostic x-ray films freed from gelatine) to the shapes of isodose curves, and stacked them, so that points which had, for example, percentage dose-rates of 60-70 had six thicknesses of film below them. Put on a viewing box, the depth of colour showed the range within which the percentage dose lay, and when one set for each beam was overlapped, the summation isodose curves could be drawn on a superimposed celluloid sheet by consideration of the depth of colour.

For a knowledge of the dose-distribution throughout a volume, a summation of dose in parallel planes is desirable. Also, if the x-ray beams are not co-planar, isodose curves in planes which do not contain the beam-axis are necessary. When the beam has circular symmetry, there are geometric methods by which isodose curves in any plane can be drawn from those in a plane containing the axis. However, Mayneord (1939a) has devised an instrument, the "dose contour projector," which enables this to be done much more easily. Flanders (1943) has described methods by which sections through isodose surfaces can be made visible by arranging a thin plane sheet of light to cut semi-transparent models. The isodose curves in the required section can be sketched in with the aid of a camera obscura, and this method can be used with beams which have not circular symmetry.

Another instrument devised by Mayneord (1939a) is the "dose finder", which aids in a study of dose-distribution in three dimensions. A dummy applicator is adjusted to a shell moulded to the shape of the part of the body under treatment. The shell is then moved 20 cm from the applicator, into which is plugged a plane carrying isodose curves (when there is circular symmetry), so that they occupy the correct position in space in relation to the applicator. A rod, with pointers at right-angles 20 cm apart, is so arranged that when one pointer is adjusted to a chosen point in the shell the other pointer gives the corresponding position in the region of the isodose curves. The plane carrying these curves is rotated about its axis until the pointer touches it, and the dose is read at the point of contact. Rectangular fields can also be studied with a slightly more complicated arrangement (Wilson, 1942b, Mayneord, 1943b). Light-beams have been used instead of mechanical pointers (Spiers, 1940, Wilson, 1942b). From a study of each field in turn, the dose-distribution due to a number of beams can be plotted in a number of parallel planes through the treated region. These can be drawn on glass plates, which also carry anatomical drawings, and stacked in correct relation to each other, so that a three-dimensional representation of the dose-distribution and anatomical features is obtained (Mayneord, 1943b).

Means of Realizing a Desired Dose-distribution

If the paper plan of fields to produce a chosen distribution of dose is to be successful, the fields must be applied to the

patient accurately. Various appliances have been devised to make this easier and quicker. First, the centre of the region it is desired to treat must be located radiographically—by relating it to bone or soft-tissue shadows, by insertion of an inactive gold seed, skin clip, small balloon-catheter containing iodine, lead-shot catheter, lipiodol, or gelatine-barium pellet, or by barium- or thorium-air contrast, according to the site. Skin markings are used to give two lines which intersect at this point. Or the vertical depth below a skin marking can be found by standard radiographic methods. This localization must be done with the patient in the exact position he is to occupy during treatment (Green, 1943).

The x-ray tube can then be set to angles measured by a "parallelogram beam director" or "arc beam director", which is removed before adjustment of the tube, or to lines scribed on a protractor spanning the patient, or arc attached to the tube. Simplest of all, a sheet of cardboard is cut to fit the contour of the body, and the lines along which the applicator should be directed are drawn on it.

A second method is the use of a calliper, fixed to the tube, which carries a pointer co-incident with the beam-axis, which can be made to slide to touch the patient at the point of emergence. Green's calliper will also indicate points at known distances normal to the beam-axis—a help when setting glancing fields—while Grimmer has adapted a calliper to give audible warning if the patient moves appreciably from the correct setting (Ellis, 1943, Wilson, 1943b, Dobbie, 1943, Grimmer, 1943, Green, 1943).

Mayneord (1939b) has described an optical device which shows the exit-point of the beam-axis by a light-spot on the patient. A small lamp can be arranged in an applicator to give a beam of light along what is later the x-ray beam axis. A tube with cross-wires and sighting-aperture, at the other side of the room, is aligned with this light-beam. The tube can also throw a light-beam back in the same direction, so that, when the patient is adjusted to the applicator, a light-spot on the patient shows the position of emergence of the beam. The use of this appliance in the treatment of oesophageal growths is described by Adams (1939). It eliminates error due to whip in mechanical callipers, but has the disadvantage that the patient must be adjusted to the applicator, which must not be moved out of line with the light-beam.

By "jig" is meant an appliance which can be fitted to a patient in a reproducible position, and which has surfaces or sockets in correct positions, to which the applicator is adjusted. A simple illustration is the jig to ensure that two wedge-fields are applied to a patient correctly at right-angles. The jig is formed of two "perspex" (a transparent plastic) plates, each the size of the applicator end, and fixed at right-angles to each other. It is adjusted on the patient so that the block of tissue it is desired to treat is within the right-angle. Skin markings are made so that it can be replaced in the same position. A metal replica is substituted for the perspex one, and any space between it and the skin is filled with "radium compo" (see below), a thermoplastic material. The radium-compo mould is detached from the metal replica, and used in the same position in the perspex jig. The fact that the radium-compo has taken the shape of the body, together with the skin markings, makes it easy to replace the jig in the same position for each treatment. It is a simple matter to bring the x-ray-tube

applicator into contact with each plane surface in turn.

Flood & Smithers (1939) illustrate a nose built up with a wax mould to form a parallel sided slab to aid in the correct adjustment of two opposed fields.

Another method is to produce a rigid shell, to fit the part of the patient's body under treatment, from plastic materials—nitrocellulose, plaster bandage, or bexoid—and to cast on it wax sockets into which the applicator will slip in correct positions (Dobbie, 1943).

The radium-compo or wax not only helps in the correct fitting of the jig to the patient, but also fills up air-spaces with tissue-like material, so that the standard isodose charts give the correct dose-distribution.

It is also necessary that the correct quantity of dose should be given to each field. Frequently this is done by making a daily measurement of the x-ray output of the tube, and then controlling the doses by stop-watch and adjustment of the tube milliamperes and kilovoltage. The latter are often difficult to keep in correct adjustment, especially when radiographers must watch more than one tube, and the switching on and off of tubes affects the line-voltage. The aggregate error in a dose may be considerable, and can be avoided by the use of an integrating dosimeter with an ionization chamber built into the master-cone of the tube on to which the various applicators fit. Such a dosimeter has been developed by Farmer (1944).

Theory and Practice

It is evident from the above discussion that much effort can be spent on the study of dose-distributions based on sets of isodose curves. It is therefore well to consider to what extent the actual dose-distributions obtained in the human body may differ from the charts. The latter are usually based on measurements made in water, so that one step is to consider what differences are to be expected in the body. However, although in the ideal, water-phantom measurements should be made for each individual tube and applicator, in practice this is too time-consuming, and usually a radiotherapy centre assumes that published charts of depth-dose values for the same quality of radiation, focus-skin distance, and field area, will apply. Tables of depth-dose values based on a survey of published values have been compiled by Mayneord & Lamerton (1941) and by Qumby (1944).

There are considerable differences between British and American values. This may be due to the use of different phantom-materials—pressedwoods, wax, and rice-flour, in addition to water, to different types of ionization chambers—the thimble chamber and the extrapolation chamber (Failla, 1937), or even, perhaps, to the prevalence of a different type of tube in the two countries. Oil-immersed tubes, where the beam emerges through a layer of oil, seem to give a more rapid diminution of dose-rate with distance, near the tube, as the oil, by scattering, acts as a secondary source nearer than the focus. Spiers (1943) has compared the behaviour of a number of materials with water, as phantom-materials. Paraffin-wax and rice-flour differed in the 200 kV range, and pressedwoods in the 100 kV range (Braestrup, 1944). The most suitable substitute for water (suitable also for the filling of scatter-bags) for the

200 kV range was a mixture by weight of about 60% rice-flour and 40% sodium bicarbonate

When jigs are fitted to the body with wax moulds it is important that the wax should behave towards the x rays in the manner of water. Some of the dental waxes are much too absorbent, being loaded with elements of relatively high atomic number. If a dosimeter is immersed in a water-phantom, and a piece of wax, etc., be interposed between the dosimeter and the x-ray source, the change in dosimeter reading is an index of the difference of the wax from water. Slabs 3 cm thick gave the following diminution of dose-rate: parabar (gum kauri, stearine, and magnesium silicate), 12%; perspex, 4%; radium compo (gum kauri, stearine, and charcoal powder), 1.7%.

If it is desired to use isodose charts in the study of treatment of parts of the body of smaller dimensions than the phantom, e.g., the neck, then the body must be built up with scatter-bags approximately to the full size. Reinhard & Goltz (1945) have studied the changes produced by the lack of an adequate thickness. With radiation of 0.9 mm copper HVL, about 5 cm of material beyond a point of measurement is necessary to give adequate backscatter there, differences could be observed 8 to 10 cm preceding the exit-surface. The exit-doses were less than those in a deep phantom by 20% for a 10 cm thickness, 29% for a 20 cm thickness, and 16% for a 30 cm thickness.

Sometimes a better dose-distribution can be obtained by discarding scatter-bags. Reinhard & Goltz (1944) have shown how isodose curves for beams incident at an angle to the skin, are affected by omitting scatter-material from the wedge-shaped space between applicator and skin. Considerably greater depth-doses were obtained towards the margin of the beam remote from the applicator-edge in contact with the skin.

Even though it is not possible for a radiotherapy centre to explore, in a water-phantom, all the fields used, a few check-measurements should be made, as wide deviations from published values may occur. It cannot even be assumed that an applicator-end is filled with radiation, sometimes strips as wide as 1 cm at the sides are almost devoid of radiation. This might be particularly detrimental when glancing-field techniques are used. Studies of the distribution of dose-rate in air across various fields have been published by Thyssen (1945), Jacobsen (1943), and Atlee & Trout (1943). Sometimes fields are badly asymmetric. Ways in which these can be improved by specially-designed filters have been described by Spiegler (1945), Meredith & Stephenson (1943), and Flood & Smithers (1939).

There still remains the possibility that dose-distributions in the human body may differ from water-phantom measurements. The bones are more absorbent, particularly of the radiations of longer wavelength, and beams which are tangential to, say, the ribs or skull, are likely to be considerably affected. The lungs and air cavities, on the other hand, will give a greater transmission than water. Quimby, Copeland & Woods (1934) made an extended series of measurements with 200 kV radiation filtered by 0.5 mm copper and 2.5 mm aluminium, both in a cadaver and in the

vaginas of patients who were irradiated both from the anterior and the posterior surfaces of the pelvis. Backscatter factors agreed well with water-phantom values for all fields of irradiation. Depth-doses in the pelvis were also in agreement, but through the chest they became progressively greater. Measurements in the thigh agreed with water measurements until the bone was reached, beyond which they were up to 30% less. Measurements of radiation transmitted through the head of the humerus also gave definitely lower depth-dose values.

The present author has measured the transmission of radiation of quality 0.9 mm copper HVL passed antero-posteriorly through the mid-region of a patient's lung. A dosimeter sandwiched between the applicator and chest wall measured a backscatter factor of 1.33, compared with the water-phantom value 1.31. The dosimeter was then arranged at the beam's exit-point on the posterior surface 17 cm from the applicator, and scatter-bags were packed around it to give a measurement comparable with that at a depth of 17 cm in a water-phantom. The depth-dose was 20.5% compared with 11% in water. The fact that the backscatter factor was unaltered suggests that the diminution of scatter from any particular part of the lung is compensated by the less absorption of this scattered radiation on its way to the point considered. Accordingly, it is assumed that any point in the lung will receive the same amount of scattered radiation as the corresponding point in water, but the primary beam will be less absorbed. If the primary beam has passed through a distance d cm of lung tissue of density ρ g/cm³ this is equivalent in absorption to only ρd cm of water. The radiation which reaches any point in the water-phantom can be divided into primary and scattered radiation by the method of Meredith & Neary (1944). At 17 cm deep in water, a surface-dose of 131 provides a primary beam-dose of 2.20 and a scattered radiation-dose of 12.8. The absorption coefficient in water of the primary beam is 0.19 cm⁻¹, and if we assume there is a 12 cm path in lung tissue of density about 0.3 this is equivalent to 3.6 cm of water. Therefore the primary beam value 2.20 must be increased by a factor $e^{+0.19 \times 3.6} = 5.44$, i.e., it becomes 12.0. The total dose should therefore be 24.8, and the corresponding depth-dose 19%. This agrees reasonably with the measured value 20.5%, and suggests that this method could be used to deduce doses in lung tissue.

Conclusion

It has been the purpose of this paper to survey what seem to the physicist the best technical methods in x-ray therapy. However, they have been developed in many centres, and it is doubtful whether there is any one centre which employs, as a routine, a very large proportion of them.

Each radiotherapist develops his own methods. There are, for example, many skilled radiotherapists who prefer to direct the beam by judgment, using no special device, except, perhaps, to indicate the position and direction of the central ray. It may be argued that physical methods can be developed beyond the clinically useful point, and readers should refer to a communication by Jacobs (1939) on this question.

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ON TECHNICAL METHODS IN RADIUM THERAPY

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Technique in the therapeutic use of radium has been developed as a result of the changing outlook of the therapist. Surgeons were quick to employ radium when proper appliances had been devised for containing and manipulating this substance, but the tendency now is towards a diminishing use of radium by surgeons for implantation into the tissues. Dermatologists were no less ready to treat lesions of the skin with preparations of radium that could easily be applied to the surface of the body. By suitable choice of metal enclosure the therapist could carry out this kind of work with beta-plus-gamma or pure-gamma radiation. This technique survives, but it is unusual to use beta-ray sources except for lesions which are essentially skin lesions. Gynaecologists have been perhaps the most outstandingly successful of radium therapists, because their work has led to far less actual surgery in uterine cancer, and the miseries of uterine haemorrhage promise to be a thing of the past.

The advances in technique fall into natural groupings which have been determined in one of two ways, e.g., a new technique may be developed as the result of a new medical point of view, for instance, the substitution of surface for interstitial applications largely arose from the view that damage to the tissues was to be avoided at all cost, or again, a new technique was developed as a result of the ingenuity of physicists in preparing radon sources which can sometimes be used in preference to radium. But no amount of ingenuity in itself can make any headway in treatment unless it is embodied in an instrument or in a process which convinces the therapist of its undoubted utility and safety.

External Irradiation

The range of this method varies from the application of

a few milligrams in the form of a capsule to the use of 10 grams at a time. At the present time considerable diversity of opinion exists about the utility of these gram units (the use of the deplorable term "bomb" for these units is happily declining). What need is there for mounting 5 or 10 grams of radium into a single unit as a gamma-ray source when this type of radiation can so nearly be duplicated by x rays? The argument may, however, be presented with equal logic the other way round, why go to the trouble of installing complicated and expensive apparatus which will almost certainly have to be discarded after 10 years' service, when one can have a most useful source of radiation requiring little apparatus and a minimum of servicing by a staff of engineers, a source, moreover, that shows an inappreciable decline over the same period of time?

As a matter of fact, there are very good reasons why one source does not exclude the other. It is true that the quantitative yield of penetrating x rays from a modern tube at a quarter of a million volts far exceeds that from a 10-gram radium unit (perhaps 10 times as big), but the latter has many advantages. It is often easier to apply to the patient, it is especially suitable when repeated and prolonged treatments are needed, and its servicing is so effective that one can almost say that these units do not suffer from breakdowns. So it may reasonably be expected that these units, ranging from 1 to 10 grams of radium, will become more and more used, provided that the present downward trend in the cost of radium continues.

Intra-cavitary Irradiation

The introduction of radium (and radon) into the natural cavities of the body when they are the seat of disease has been developed on lines which ensure as far as possible an adequate dose to the malignant regions with no overdose to the normal contiguous structures. This is most successfully done, perhaps, in the treatment of cancer of the uterus and in buccal cancer, but when growths originate in the rectum or oesophagus there are greater difficulties in ensuring the necessary conditions.

In the treatment of uterine cancer, radium is put into the body of the uterus, the cervical canal, and the fornices, by means of special applicators containing radium in platinum thick enough to ensure that practically homogeneous gamma

rays are being used. Supplementary to this disposition of the radium, every effort is made by the use of packs to keep the normal tissues well away from the zones of most intense irradiation. This is also attempted when radium is applied to the rectum in cases of malignancy, one of the most successful appliances is that devised by Margaret Tod, who arranged the radium inside a pneumatic device which could be expanded *in situ*, this helps to push the normal structures away from the irradiated zones.

For growths of the oesophagus, the device of Souttar allows the introduction of radium into the lumen of the oesophagus, but immediate contact is prevented by means of a Souttar's tube, which holds the radium axially. A valuable measure of control and protection is afforded by this device.

Interstitial Radium

Dominici was among the first to introduce radium enclosed in platinum into the tissues, the method was developed so that large volumes of tissue such as occur in mammary cancer were penetrated at many points by radium tubes 6 cm. or more in length with a diameter of several mm. An extensive though not uniform irradiation of the malignant process occurred under these conditions, but the disadvantages of the method, with its associated trauma, brought interstitial work into disfavour, and to-day it is probably true to say that if radium therapy can be carried out without recourse to interstitial methods then it is so done. But nevertheless there are several sites where such methods are still the best, for instance, lesions of the tongue where, owing to involuntary movement, it is almost impossible to use any other method properly.

No account of interstitial methods in treatment would be complete without mention of radon technique. The gas from radium can be purified so completely that one can handle quantities that represent extreme purity, the volume of 1 curie is just less than 0.6 mm³, and one gram of radium in solution can yield 25 curies during the course of a year, so that the total volume of pure gas is only 15 mm³, the refinements of technique allow this to be shared among no less than 10,000 capillary tubes which, when mounted in platinum, serve as gamma-ray sources, their lengths ranging from 5 mm. to 3 or 4 cm.

In any technical discussion upon the use of radon it soon becomes apparent that, in spite of contra-indications, it continues to be used because objections are outweighed by advantages. It can be said that the outstanding advantage is the adaptability that attends its use, in other words, the size, shape, content and filtration can be altered to suit the clinical need of the moment, moreover, radon "seeds" can be inserted into the tissues and left there without danger to the patient. Against this we have the decline of its activity, which renders it unsuitable for treatment which lasts more than a few days, the high cost of running a radon centre, and the danger to technicians engaged in the work of purification and concentration of the radon.

Therapeutic Aims and Methods

The three outstanding technical methods of using radium (and radon) in treatment have been discussed. It remains to say something of what is the aim behind these methods. Whatever the radiotherapeutic method in treating malignant disease, the aim is certainly to destroy all malignant cells,

but it is equally certain that in many cases this is quite impossible if any regard is paid to the normal tissues of the body of the patient. In most cases this is due to the fact that growths are ill-defined in their extent, and this being so, it is evident that unless irradiation is extended well beyond the probable limits of the growth, some of the malignant cells will escape. We are, in fact, dealing largely with probabilities, not certainties, in the treatment of malignant disease, and an experienced radiotherapist is more likely to discern these probabilities than an equally clever but less experienced one. On this basis, it is evident that technical methods are developments of ingenuity in the best means of balancing the manifold considerations that are involved in the irradiation of a malignant growth.

There is indeed a wide difference in outlook between those who, for instance, plan an extensive irradiation of a breast-tumour by the implantation of radium needles, and those who seek the same end by the use of externally applied gamma radiation which can be repeated at intervals determined by the day-to-day response of the organism. It is the latter working philosophy which originated in the French School, and which has been given a rather different orientation by the work of Spear and his colleagues of the Strangeways Laboratory, Cambridge, here, in fact, is a technical method which combines the virtues of sound biological intuition with the asset of rigid physical control.

If technical methods are to be improved, there must be a happy balance between biological probabilities and physical certainties, it is well, however, not to insist too much on the latter. Isodose curves are usually derived from measurements upon media having about the same density as the average of the tissues concerned in treatment, but there need be no insistence on the general crudeness of any such similarity. Any assessment of the differential response of the various structures of the body to irradiation is a matter not for the physicist but for the radiologist. It need not be emphasized that judgment upon this crucial matter will depend not only upon the clinical sense of the radiotherapist, but on his pathological knowledge. It is one of the greatest claims to eminence in the field of radiotherapy, that the French School, led by Regaud, and now by Lacassagne, has so persistently maintained that this pathological knowledge, not only of the nature of malignant growths but of their individual reactions to irradiation, should be the basis of the scientific method.

A few words may be said about technical methods in radium therapy other than in malignant disease. One of the most successful applications is in the treatment of uterine haemorrhage, and it is somewhat remarkable that, in spite of the generally good results obtained, there is a considerable difference in the dose employed at different clinics. Early in the study of this condition it was found that the dose required to bring about a cessation of the dominant symptoms varied with the age of the patient. The following quotation is taken from Elizabeth Hurdon, *Cancer of the uterus* (London, 1942).

"The treatment of simple metropathic haemorrhage depends partly upon the age of the patient, but the severity of the anaemia due to haemorrhage, and the presence of myomata, have also to be considered. The cases are divided into three groups in relation to the age incidence and the reproductive function.

Group I Adolescent cases—patients under 20 years of age

Group II Child-bearing period—patients from 20 to 40 years of age

Group III Includes the menopausal, 40 to 50 years of age and post menopausal cases

Typical doses for each age group are as follows

Group I 250 to 300 mg hr

Group II 600 to 750 mg hr

Group III 1,100 to 1,200 mg hr

Screenage is 1 mm platinum and 1.5 mm rubber "

It will be seen that the biggest dose found necessary in the treatment of this condition is 1,200 mg hours (50 mg for 24 hours), yet there are many British workers who consider that treatment is not adequate with less than 48 hours' exposure, using 50 mg of radium. The question arises, in view of the fact that the technical methods are practically identical, as to why this wide disparity of doses continues to operate. If the bigger dose is indeed necessary, how is it that 97% of the menopausal cases cited by Hurdon remained well without further treatment? On the other hand, if the shorter exposure is adequate, what purpose is served by a more severe one?

Technical Methods in the Future

The methods which have been most highly developed technically up till now are the methods developed in the use of the gram units and in the use of radon, both big and small quantities call for specialization in design and management

Advances in pure science in the last 15 years have shown the feasibility of making ordinary substances radio-active, and the time may soon be at hand when these will be used in medical treatment as well as in research. Advances in applied science during the last year have drawn attention to the possibilities of using atomic power on a more liberal scale than we have so far enjoyed. Mere power, however, has not the first claim in the selective list of requirements among radio-therapists, what is primarily wanted is some form of energy which will give a wider margin of response between normal and malignant tissues, and at the same time be easily adapted to the purely technical demands of those called upon to treat malignant growths in any part of the body

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MILLION VOLT THERAPY

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Up to the year 1930, the maximum voltage x-ray equipment available for x-ray therapy was of the order of 200 kilovolts. With such equipment it had been demonstrated that in some types of cancer it was possible to attain a cure without irreparably damaging the patient. It was not known whether the failure in many lesions in certain sites was due to a difference in radiosensitivity, or whether it was due to the impossibility of delivering a sufficiently high dose to the lesion. The problem was not a simple one, being complicated by many factors.

No matter how high a dose is administered to a lesion, there are always some malignant cells left intact, and these have to be overcome by local normal cells if the lesion is to be eradicated. This can take place only if the normal cells have been less damaged by the radiations than have the malignant ones—that is, if the normal cells are less radio-sensitive. Whether this radiosensitivity factor varied with the wavelength of the radiations was not known, but the hope that this might be the case warranted investigation into the unexplored shorter wavelengths.

For optimum results, damage to the normal tissue surrounding the malignant zone should be reduced to a minimum, otherwise blood-supplies to the normal cells in the zone of destruction will be cut, reducing their effectiveness. This requires a rapid decline of the x-ray dose outside the zone of required destruction, and it was forecast that this could be accomplished with the shorter wavelengths, due to the sharper delimitation of the beam edges.

A third factor arises which might be called the patient's vitality, over which the therapist has only some small control, namely, in making certain that the total radiation energy absorbed by the patient is a minimum commensurate with

the necessary lesion dose.¹ Providing that all stray radiations have been excluded, the energy absorption during the treatment then becomes a question of the most effective geometric distribution of the required x-ray beams, both physically and clinically, and of the physical properties of the radiation used.

Treatment at wavelengths shorter than those obtained with a 200 kV equipment had been carried out in the use of radium on surface lesions, interstitially, in body cavities, or in mass in the radium-bomb units. The nearest approach to the methods employed in x-ray therapy are those of the radium bomb. The main difference is that owing to the low gamma-ray output from radium bombs, treatments can be carried out only at short distances from the patient, limiting the use of the bomb to lesions at short distances from the skin surface. In order to obtain the same radiation intensity as that emanating from a 200 kV tube operating at 10 mA 40 cm FSD [Focus-Skin Distance], 1.0 mm copper HVL², 1,000 grams of radium would be required.

However, it had been established from theory and experiment that the shorter the wavelength of the x rays—that is, the higher the voltage applied to the x-ray tube—the more penetrating the rays would be and the less the absorption would vary with the density of the medium. One of the problems in 200 kV therapy was, and is, the distortion, due to intervening bone, of the theoretical dosage-distribution by an unknown factor. With the shorter wavelengths this unknown factor should become less disturbing.

X-ray Equipment Some Technical Considerations

By 1933, a few experimental high-voltage x-ray equipments had been constructed in the USA, operating at voltages up to one million, but they were too unreliable in operation to give biological and clinical results which could be assessed. Usually these tubes had at the most only two fixed beam-

¹ The lesion dose is the average dose throughout the lesion specified in röntgens. It is estimated from a mathematical analysis of the dose-distribution in the patient arrived at by the summation of dose-distribution charts for each x-ray beam. These charts are obtained by ionization-chamber measurements in a water phantom.

² Half Value Layer (HVL) is the thickness of a specified material which, when introduced across the x-ray beam effectively reduces the emergent beam to one half of its original intensity.

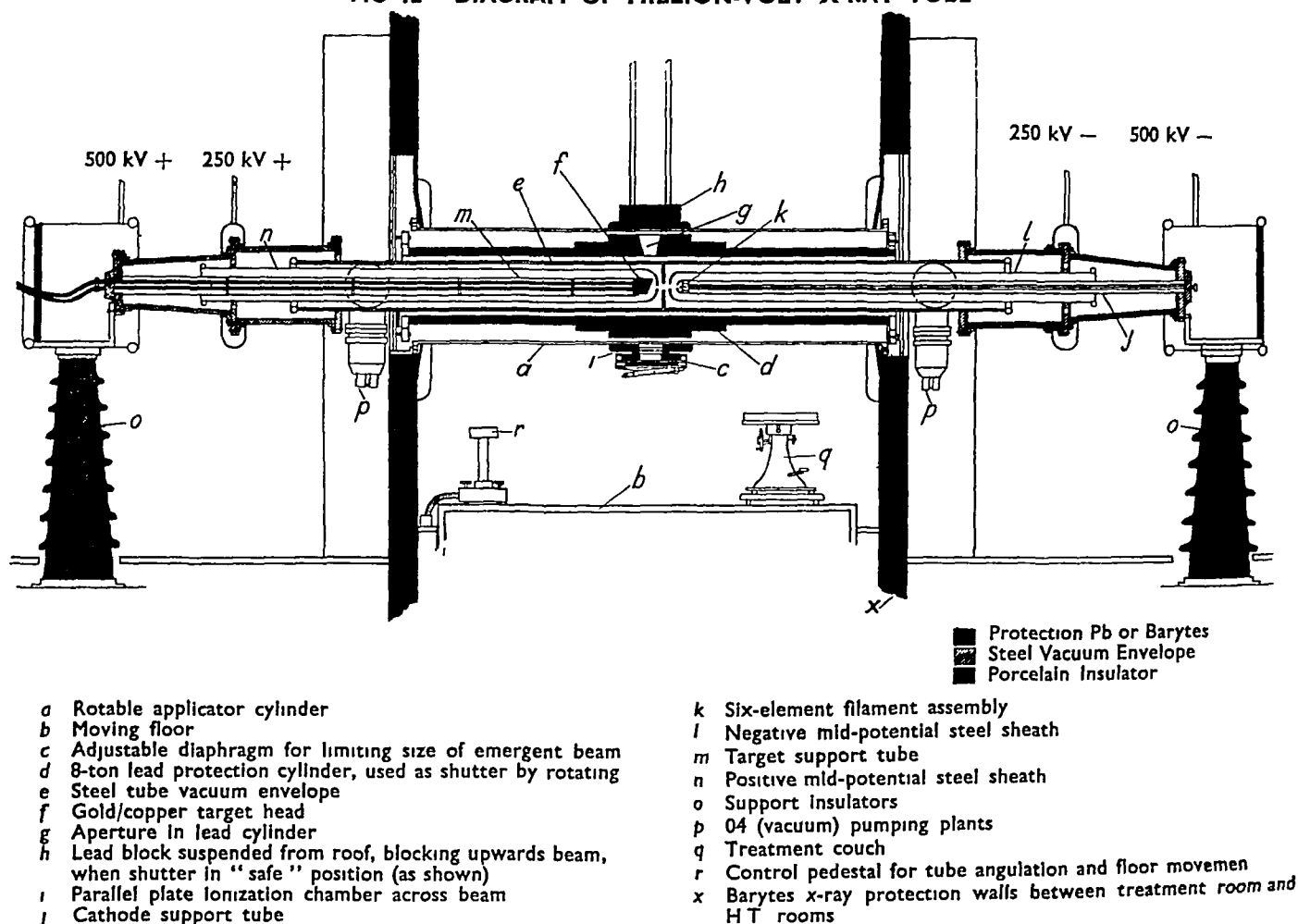
directions, necessitating tilting of the patient to the tube, in order to accomplish cross-fire techniques. This method is deprecated in Britain, since it is argued that unless the patient is prone, supine or, for a restricted number of sites, sitting up, it is impossible to know the exact position of the various body-organs. Angulation of the tube to the patient is therefore demanded as one of the essential features of an x-ray tube.

The main difficulty encountered in sealed tubes in the attainment of higher voltages was that the increased electrical stresses applied to the electrodes and envelopes extracted

department. Instead of the usual sealed-off thermionic rectifiers in the attached high-voltage generator, a pair of continuously-evacuated demountable rectifiers was fitted.

With the advent of these new oil diffusion-pumps and the demonstration that continuous evacuation was feasible and reliable, the development of high-voltage continuously evacuated tubes with walls and envelopes, electrically better than those of the sealed-off tubes, but which had previously been barred by their prolonged gassing, became an economical proposition (Allibone & Bancroft, 1934, Beetlestone & Innes, 1934, Burch & Sykes, 1935).

FIG 1a. DIAGRAM OF MILLION-VOLT X-RAY TUBE



occluded gas from them, resulting in internal electrical breakdown between the electrodes, and often in the puncturing of the glass envelope. In one or two instances tubes were supplied to withstand 350 kV, but they were never really robust.

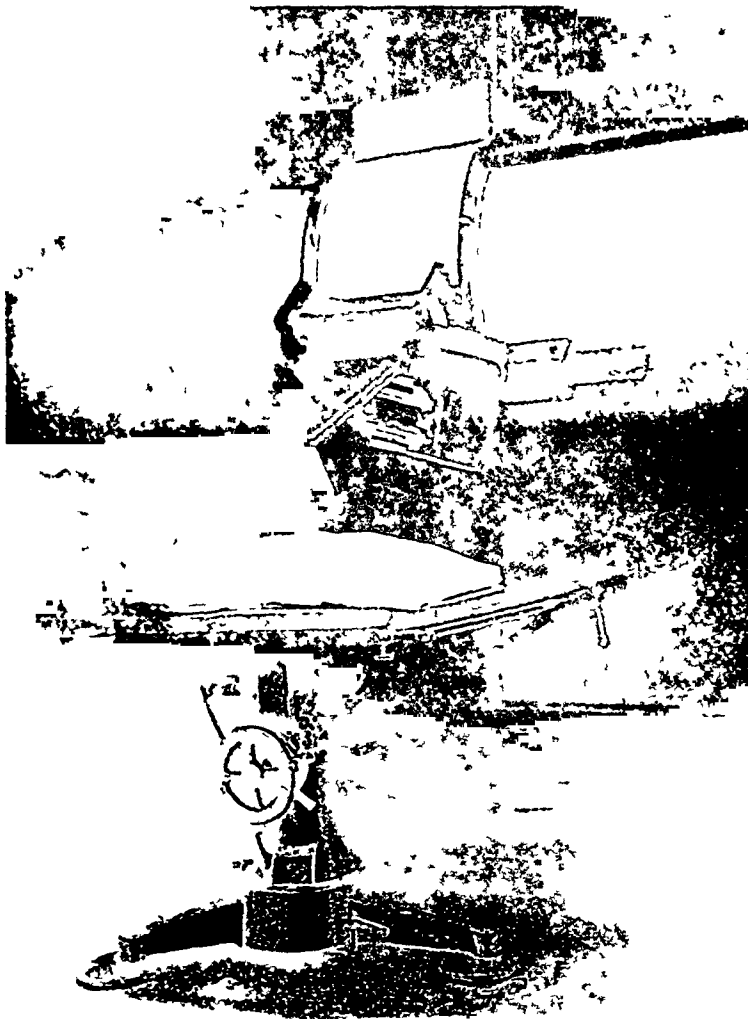
In 1932, a pair of 200 kV steel and porcelain, demountable x-ray tubes, continuously evacuated by their attached oil diffusion-pumps, were installed in Sheffield Radium Centre. The oil diffusion-pumps operated on the newly developed low-vapour-pressure Apiezon oils, and did not need the expensive liquid air-traps required on mercury-vapour condensation pumps. Continuous evacuation and demountability made possible the cheap replacement of target and filament by any mechanically-minded member of the x-ray

Million-volt Equipment at St Bartholomew's Hospital, London

The hospital is indebted to the foresight of its Radium Committee, the generosity of Mrs Meyer Sassoon, and the technical skill of the Research Department of Messrs Metropolitan-Vickers Electrical Co, Ltd, Manchester, for envisaging and making available the million-volt plant installed in the hospital in 1936. The equipment was guaranteed to operate at 600 kV DC [Direct Current] 3 mA, with the proviso that continuous operation at one million volts would be aimed at. In the first hour after final erection 700 kV 4 mA was attained, but at voltages greater than this the tube became unstable in operation (Allibone, Bancroft & Innes, 1939).

During the next two years, while many modifications and

FIG 1b MILLION VOLT X RAY TUBE



Tube in the treatment room showing the light centring device and diaphragm

additions were made to the tube, treatments were carried out at 700 kV giving the medical and physical staff an insight into the problems to be encountered at higher voltages. By 1938, the plant was operating continuously at one million volts and since then some 10,000 hours of operation have been accomplished in spite of many near misses by bomb and V-weapon. Although there was considerable damage to the buildings on many occasions, the plant suffered little and at no time were treatments not carried out to schedule, except when power supplies were interrupted.

The equipment is so designed that, as far as possible, methods of treatment previously employed at 200 kV can be repeated with the new tube. The tube (Fig 1 a, b) spans the treatment room (X-X) and from the centre of its span can emerge the x-ray beam, the direction of which can be varied from pointing vertically downwards to 110° upwards. This is accomplished by rotation of the outer sheath

of the tube (a). Adjustment of the patient to the tube beam is accomplished by making the centre part of the treatment-room floor (b) under the tube traversible vertically through 7 feet [about 2.2 m]. This is necessary since it would have been difficult to traverse the 32 feet long [about 9.75 m] tube which weighs nearly 12 tons [about 12,192 kg]. The minimum FSD obtainable with ease is 60 cm, comparable with that used at 200 kV.

Beam limitation at 200 kV is done by lead-lined boxes called applicators, fitted with end limiting stops of the required size. At a million volts and 100 cm FSD such applicators, to be effective, would weigh some 200 pounds [91 kg] and would be rather expensive and difficult to change. An adjustable diaphragm (c) was therefore fitted on to the tube outer sheath, built up of twin 1.5 inch [about 3.8 cm] thick adjustable lead stops, giving any beam size from 5×5 to 40×40 cm, at 100 cm FSD. It is possible to use the diaphragm down to 60 cm FSD but beam positioning then becomes awkward. The diaphragm has a light-beam

device attached, indicating the size and position of the x-ray beam in space. The x-ray beams obtained from the diaphragm are not perfect, since they have penumbral edges caused by combination of a large focal spot, 2.5 cm, with the position of the stops at half the distance from the focus, when used at 100 cm. The advantages, however, outweigh this imperfection, and in the future a light secondary diaphragm may be added.

Inside the outer sheath (a) on which is mounted the diaphragm, is a protective lead cylinder (d), which itself surrounds the steel vacuum envelope of the tube (e). This lead cylinder, which weighs 8 tons, gives an effective protection of 6 inches of lead in any direction relative to the focal spot on the target (f). The protection is so effective that with the tube operating at full excitation—one million volts 4.5 mA—the x-ray leakage into the treatment room is only one half of tolerance dose (10 r/sec), a degree of protection rarely encountered in 200 kV

tubes. The lead cylinder is also used as the x-ray shutter of the tube. There is one aperture in the lead cylinder opposite the target head which aperture (g) in the safe position points upwards into a six-inch-thick lead block suspended from the treatment-room roof. This block prevents the emergence of the x-rays upwards into the treatment room. Providing the treatment-room doors are shut the whole of the lead cylinder can be made to rotate by pushing a control button in the control room, and by automatic interlocks it stops rotating when its aperture is aligned to that of the diaphragm on the outer sheath so permitting the emergence of the x-ray beam in the required direction through the diaphragm stops. Just behind the diaphragm is mounted a three plate ionization chamber (h) which indicates on an instrument on the control desk either the x-ray intensity or the dose given during an exposure. Mounted on the control desk are also direct-reading kilovoltmeters indicating the actual kilovoltage applied to either end of the tube and the sum of these, irrespective of load

current. These are electrostatic voltmeters which operate from a definite proportion of the kilovoltage applied to each end of the tube, obtained from oil-immersed resistance potentiometers connected from each end of the tube to earth.

The high voltage for the tube is supplied by two 500 kV Cockcroft \pm DC generators comprising transformer, condensers, and four continuously-evacuated thermionic rectifiers each, and operating from the AC [Alternating Current] mains. All vacuum and electrical operations are indicated on a power-station type of illuminated diagram, facilitating fault-finding.

The treatment and high-tension rooms are enclosed in walls built of some 125 tons of interlocking barytes bricks, so effectively preventing the egress of x rays that it is possible to store films within a few feet of the treatment room.

In this equipment we have a simple, controllable, safe source of high-voltage x rays, not quite as hard as the gamma rays from radium, but equal in intensity, under the same geometrical conditions, to 7,000 grams of radium.

During the war no development work on x -ray tubes and equipment has been possible in Britain, but in the USA a number of different types of high-voltage x -ray equipments have been produced, one in particular being very compact tube and resonating transformer being housed in a tank some 6 feet [1.8 m] long and 4½ feet in diameter. It is also of interest to note that during the German occupation of Norway, Norwegian engineers and physicists constructed and operated a 1.5 million volt Van de Graaff generator and multi-acceleration tube.

Physical Investigations on Operating Conditions

When the treatment of patients with the million-volt plant commenced, there were few physical data available regarding the properties of the short-wavelength rays so generated, and a complete investigation had to be made to find the optimum operating conditions to attain (i) the shortest economical wavelength and (ii), at the same time, the best geometric arrangement to give the highest % depth dose in the patient, with a reasonable x -ray intensity. Since the primary object of the whole investigation was to find whether the radiosensitivity of malignant cells, *in vivo*, increased with reduction in the x -ray wavelength, the tendency was to bias (i) in preference to (ii).

The properties of generation of x rays, by the stopping of high-speed electrons by a target, are such that, although the electrons have all, in our case, a million volts equivalent velocity, the emergent x -ray beam is a heterogeneous one composed of wavelengths varying from the shortest, which has a quantum energy equivalent to that of the original electron to rays which just come through the tube wall. The peak intensity is at about 700 kV, and the mean about 450 kV equivalent. Passing such a heterogeneous beam through single or composite metal filters, the long wavelengths are absorbed to a greater degree than the short wavelengths, resulting in a hardening (shortening) of the average wavelength of the emergent beam. What is more important, however, is that the very soft (long) wavelength rays are completely removed. These cause considerable damage to the first few millimetres of tissue and as they do not penetrate further, they do not contribute to the lesion-dose.

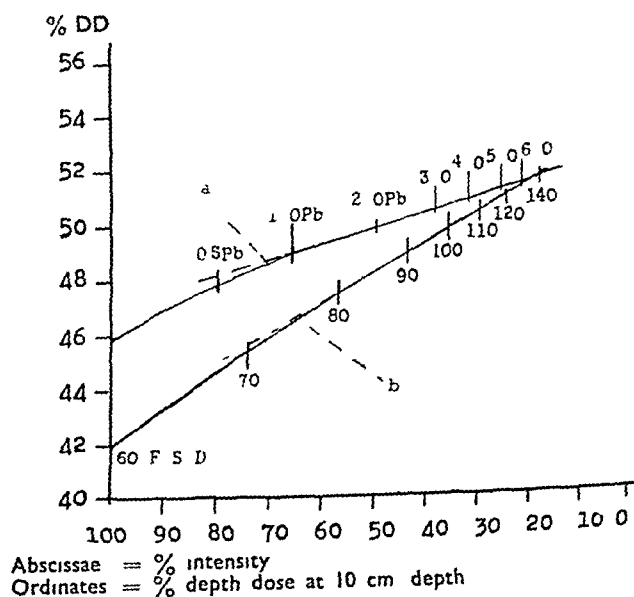
It was found that there was little difference between lead

and tin filters, the lead if anything, being slightly more efficient. Backing of the lead filter by tin and copper was not found necessary presumably since the 4.2 mm steel wall of the tube effectively removed the anomalous lead radiation (Mayneord & Roberts, 1935).

The distribution of dose in the patient is a much more complicated problem and, to simplify physical investigations it is carried out in a medium which has the same electron density as the average of all the body-components. Water is one such medium while there are others of more complicated nature (Spiers, 1943). The relationship between (a) the dose at any point in the medium to (b) the dose at the surface of the medium at the beam centre, when expressed as a percentage, is called the Percentage Depth Dose (%DD), while the chart giving the %DD-distribution in a plane by lines joining points at equal dose-level is called an isodose. The dose at a depth is made up of many components, and for general purposes here they can be divided up into three: direct beam, backscatter and forward scatter. The direct beam is that part of the dose originating from the ionization produced at the point by absorption of x rays from the part of the main beam which has penetrated to the depth. Backscatter is the dose originating from secondary x rays scattered back from the part of the medium beyond the point of measurement, while forward scatter is from secondary scatter from the part of the medium above the point of measurement.

Investigation into the variation of %DD with filtration of the x -ray beam indicated that not only was the lead filter the most efficient in increasing the %DD, but also that the maximum efficiency was between 0 and 1 mm of added filter. With heavier filters the improvement was linear but less noticeable (See Fig 2, Curve a). It will be noticed that the criterion of efficiency is the improvement of %DD in a

FIG 2. PERCENTAGE OF BEAM INTENSITY LEFT



Abscissae = % intensity
Ordinates = % depth dose at 10 cm depth

Curve a Percentage of depth dose with increasing lead filtration filter thickness marked on the curve, plotted against residual beam intensity 10 x 10 cm, 100 cm FSD, 1,000 kV
Curve b Percentage depth dose with FSD, FSD, marked on the curve, plotted against residual beam intensity 10 x 10 cm, 2 mm lead added filter, 1,000 kV

10 x 10 cm field at 100 cm FSD plotted against percentage of the beam intensity left. The improvement of the %DD with FSD is given in Fig 2, Curve b, which shows that the maximum efficiency of improvement is produced between 60 and 80 cm FSD, improvements at distances greater than this being slower but appreciable. If %DD improvement were the main object, the optimum condition would be about 0.5 mm added lead filter and as long a FSD as possible, since the efficiency of improvement is greater by FSD than by filtration at this voltage.

In our case, however, where the main investigation was whether there was an increase in radiosensitivity of lesions with reduced wavelengths, a harder beam obtained with a 2 mm lead filter was decided on, with a FSD of 100 cm, giving an x-ray output of 40 r/min, comparable with the output of 200 kV equipment.

Physical Advantages of the High-Voltage Beam

Since previous experience had been confined to 200 kV x rays, the main interest physically lay in a comparison between the behaviour of the beams in a phantom, and an attempt has been made to formulate reasons for the differences. The main improvement with reduction in wavelength is the increased penetration, but the %DD is a related feature in which variation of back- and forward scatter, FSD, depth, absorption-coefficient, and field-area all play a part, and an attempt was made to sort out these by measurement and calculation. Fig 3 gives the portions of direct, back- and forward scatter obtained as a percentage of the depth-dose on the beam-centre-line for 10 x 10 cm beams at 40 cm FSD 200 kV and 100 cm or 1 million volts. At the surface at 200 kV the dose is 11% direct, 29% backscatter, while at 1,000 kV it is 93% direct and 7% backscatter. As we progress through the beam at 200 kV, the direct-beam component decreases rapidly not only relatively, but also absolutely, while at 10 cm depth it becomes even less than the backscatter. At 1,000 kV, the backscatter component is only a small portion of the dose. The forward scatter in both cases increases rapidly and is of the same

The direct component of the beam can be represented by and is

$$I_d = I_a e^{-\mu d} \left(\frac{F}{F+d} \right)^2$$

where I_a is the air dose at the surface—FSD, F , μ , the absorption coefficient and I_d the dose at depth d , due to direct beam.

Both the backscatter and forward scatter components increase with field-area up to a maximum, beyond which any further added beam-area will not contribute to the dose, since it will be beyond the range of the scatter.

From the curves and the above, certain forecasts can be made.

(i) Since the penetration, i.e., the direct beam, is greater at 1,000 kV, and the greater portion of the dose at all depths is due to direct beam, the depth-doses will be greater than those met with at 200 kV (the forward scatters being the same). Not only will this be the case but, since at 1,000 kV so little of the dose at a depth depends on scatter, there should be little change in %DD with field-area, quite contrary to 200 kV experience, where the %DD is governed

to a great extent by the backscatter and hence by field-area. Further, the improvement with 1,000 kV will be the greater, the greater the depth. At 200 kV there is little change in %DD with FSD beyond 50 cm FSD, and this can be understood by examining the information in Fig 3. Since the direct-beam contribution is a small portion of the dose at the depth, any variation in its value due to alteration in F

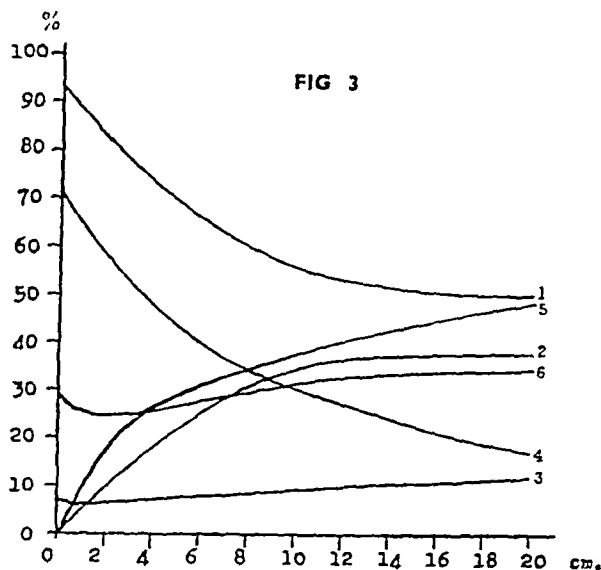


FIG 3

Abscissae = depth in cm

Ordinates = components as % of % of depth dose

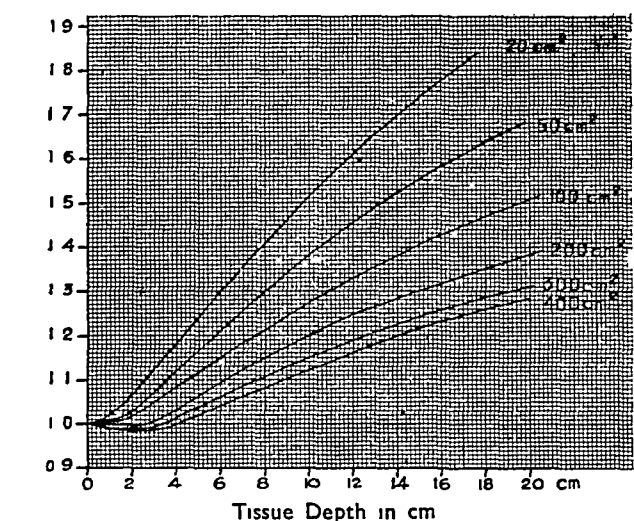
- 1 1,000 kV direct beam component as a % of the % of DD
- 2 1,000 kV forward scatter as a % of the % of DD
- 3 1,000 kV backscatter as a % of the % of DD
- 4 200 kV direct beam component as a % of the % of DD
- 5 200 kV forward scatter as a % of the % of DD
- 6 200 kV backscatter as a % of the % of DD

(in the formula) will be masked in the %DD by the small part it takes in the whole. At 1,000 kV, on the other hand, the direct contribution even at 20 cm depth is over 50% of the dose, so increases in the direct component by increase in the FSD will be appreciable in the %DD.

Fig 2, Curve b, indicates that the last deduction holds, while Fig 4 indicates that the forecasts about relative %DD at 1,000 kV and 200 kV are along the lines indicated. The gain in small field-sizes is particularly noticeable, being as high as 50% increase at 10 cm depth for a field 20 cm². This opens up many new avenues in treatment design, which will be indicated later. Even for large beams, the improvement, though small (about 12%), is of importance in many cases of opposed-field technique. Further, with the reduction in backscatter, and also since the forward scatter is, with the higher voltages, more in the forward direction, the high-voltage x-ray beams show a much sharper delimitation on the geometric edge of the beam and a flattening of the isodose contours.

All these physical improvements make possible many alterations and refinements in techniques developed for 200 kV therapy, and some methods quite inapplicable at 200 kV have been introduced. There is one other factor which has to be brought in, out of sequence, before it is

FIG 4



Abscissae = tissue depth in cm
 Ordinates = ratio $\frac{\text{tissue dose 1,000 kV x rays}}{\text{tissue dose 200 kV x rays}}$

Ratio of the tissue dose with 1,000 kV DC x rays (9.0 mm Cu HVL) to that with 200 kV DC x rays (2.0 mm Cu HVL) for the same input skin dose at 100 cm FSD and various field sizes

possible to discuss alterations in treatment technique, viz, skin reaction

Alteration in Skin Reaction

Tests were carried out on corresponding skin surfaces on patients with x-ray beams of identical dimensions under the same physical conditions except for the beam qualities. The control beam was one of 300 kV (3.35 mm Cu HVL), while the experimental beam was 1,000 kV (10 mm Cu HVL). The dose required in one sitting to produce the same skin reaction was 50% greater with the 1,000 kV than with the 300 kV beam. Theoretically, only part of this alteration in skin response can be accounted for by the reduction in the photoelectric absorption in the sulphur in the skin with the shorter wavelengths, the remainder being so far unexplained, unless it is due to a radiosensitivity change. The results conform well with those encountered in gamma-ray treatment. This reduction in skin response also opens up improvements in technique, but more especially makes possible a reduction in the skin reaction which has undoubtedly an indirect effect on the patients' well-being, during and after treatment.

Modifications in 200 kV Techniques possible by employing Million-volt X Rays

1 Whereas it was impossible to employ small fields in the treatment of small lesions buried deep in the body (e.g., rectal carcinoma), owing to the poor depth-dose of such fields, at 1,000 kV, it becomes possible and economical to employ multiple small fields, even through the remote lateral skin surfaces.

2 In intrinsic carcinoma of the larynx, it is customary and necessary at 200 kV to employ three fields—two opposed laterals, and an anterior field. At 1,000 kV only the two opposed laterals are necessary, which simplifies and increases the accuracy of the technique.

In this type of case with two opposed beams, it is found that blocks of tissue up to 14 cm thick receive nearly uniform

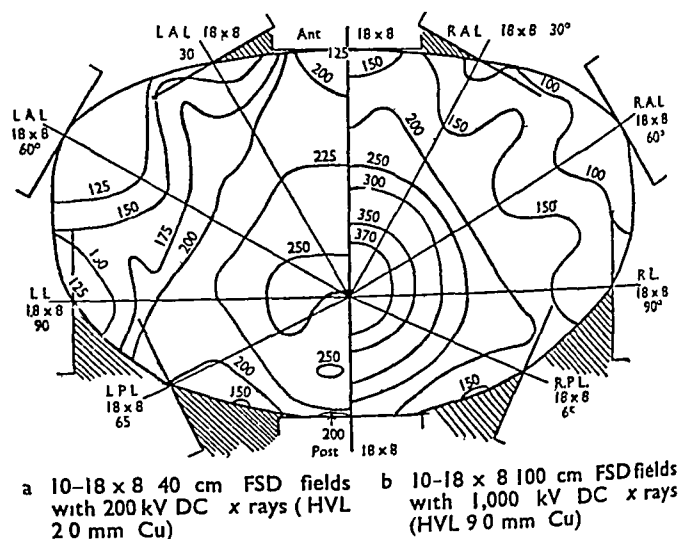
irradiation throughout by two opposed million-volt x-ray beams.

3 In many cases at 200 kV it is found necessary to employ beams angulated in three dimensions (spinal cord and bladder). So far, at 1,000 kV, it has not been found necessary to employ such beams except in a few brain cases where the eye has to be avoided. Setting up beams accurately in three dimensions and calculating the necessary isodoses is a difficult process, and one which should be avoided unless the most elaborate equipment and calculating devices are available.

4 Where originally at 200 kV it was quite impossible to attain a uniform and sufficient dose owing to the patient's size (e.g., carcinoma of the breast of a large woman), even with the small increase in depth-dose in large beams at 1,000 kV, few cases have been encountered where it is impossible to administer a greater uniform dose to the lesion than to the skin.

5 Where, at 200 kV, lesions have had to be approached by beams through organs, the damaging of which incapacitates the patient (e.g., glancing beams in carcinoma of the oesophagus damaging lung-tissue), at 1,000 kV, most of the lesion-dose can, because of the increase in depth-dose and the reduction in skin response, be contributed by the anterior and posterior fields, leaving only a small portion to be administered by the glances through the lung.

FIG 5 ISODOSES ON A TRANSVERSE SECTION OF A CARCINOMA OF THE RECTUM



a 10-18 x 8 40 cm FSD fields with 200 kV DC x rays (HVL 2.0 mm Cu) b 10-18 x 8 100 cm FSD fields with 1,000 kV DC x rays (HVL 9.0 mm Cu)

Comparison of the Physical Data obtained for Treatment of Carcinoma of the Rectum

Fig 5 gives the cross-section outline at the level of the pubic crest in the case of carcinoma of the rectum. This type of case has been chosen because it shows very well many of the advantages of million-volt therapy, when compared with 200 kV therapy. The case is treated with ten 18 x 8 cm beams at the angles indicated, each field being given 100 units of x rays on the skin. On the left half of the section is shown the isodose if the case is treated at 200 kV with the usual 40 cm FSD and Thoraeus filter. On the right-hand side

is the isodose if the patient is treated at 1,000 kV 100 cm FSD, 2 mm lead filter (HVL 9.3 mm Cu)

The differences are obvious. The lesion, which is a small one, is surrounded by the 370% contour at 1,000 kV and by the 250% contour, approximately, at 200 kV, indicating a 50% improvement with 1,000 kV rays in the lesion-dose, for the same input-dose on each field. Outside the lesion the dose declines rapidly at 1,000 kV, whereas at 200 kV, even up to the skin, the dose is still 80% of the lesion-dose, unnecessarily causing damage to normal tissue and disturbances to the patients. The maximum skin dose is the same in both cases. If, now, 6,000 r is to be given to the lesion in 5 weeks, the following results are obtained

Dose	1 000 kV	200 kV
Lesion-dose (5 weeks)	6 000 r	6 000 r
Dose per field	1 620 r	2 400 r
Dose/day	650 r	960 r
Maximum skin-dose	3 400 r	5 030 r
Integral dose ¹	40 Mgr	65 Mgr

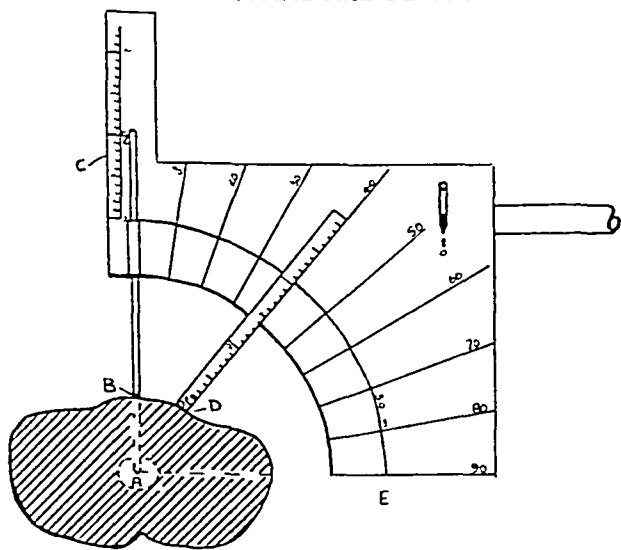
It is doubtful if it would be possible to attain 6,000 r at the lesion, at 200 kV, since the skin dose is probably above the tolerance, also the dose per day is high and would impair the patient's vitality. The integral dose is a measure of the dose absorbed by the patient, being the sum of the products of volumes of tissue and their respective doses. 40 Mgr is nearly the upper limit and it is doubtful if many patients would survive 65 Mgr.

Similar conclusions can be arrived at for other lesion-sites, and as a matter of routine all cases are isodosed at a million volts, each case being treated as an individual case with its individual problems.

Effect of the Variation of Density through the Body

Considerable investigation has shown that at 200 kV the isodose curves calculated for treatments have always erred

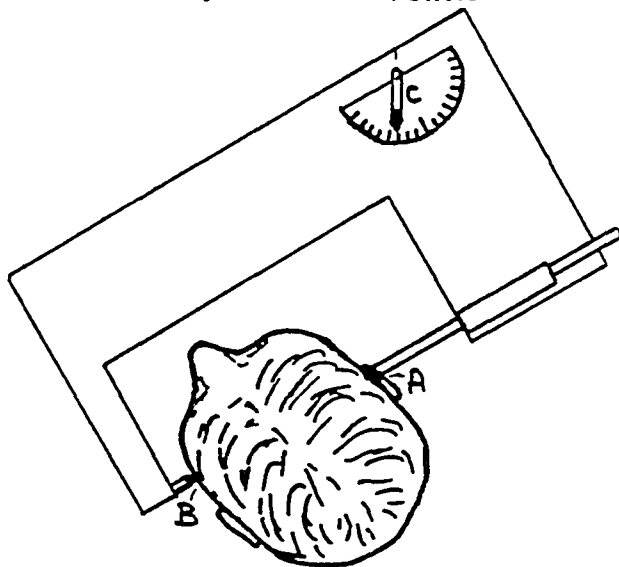
FIG 6 PIN-AND ARC DEVICE



on the optimistic side, particularly where beams have had to pass through bone. At 200 kV a particular skull absorbed

¹ Megagramme röntgens

FIG 7 DEVICE FOR MEASURING THE ANGLE OF A LINE JOINING TWO POINTS



15% more than the same thickness of tissue, while at 1,000 kV there was only 4.5% more absorption. This would mean that in the treatment of a brain tumour at 200 kV the lesion-dose might be at least 15% lower than calculated. A particularly bad case came to light in an investigation into distribution, in the course of post-operative radiation in carcinoma of the breast, where, at 200 kV, the measured dose was 1/3 of that calculated, mainly due to the fact that the angles of the beams, at that particular point, were the same as the ribs.

At a million volts, discrepancies have been small and rarely more than 10%. This may be partly due to the fact that so little of the dose at a depth depends on scatter, and the surrounding conditions do not therefore affect the dose to any appreciable degree.

Because of these discrepancies, there is sometimes a tendency to feel that the complicated and sometimes laborious calculation of the theoretical distribution of radiation is unnecessary. It must be pointed out that the cases quoted are the worst encountered and that unless investigations commence from some mathematical basis, particularly when analysing a group of similar cases, it will be impossible to draw any dosage conclusions, or to attempt by models to simulate the actual patient and so solve the troublesome features mathematically. At a million volts the variations are disappearing, and an assessment of results of different geometric methods of treatment is considerably helped by a full physical investigation.

Aids to Accurate Technique

The light-beam indicating the position and size of the x-ray beam can be made to travel along the axis of the tube and, by rotation of the outer sheath of the tube, at right-angles to the tube-axis. These two movements are often of assistance, giving an accurate idea in many cases of the position of the emergent beam. Beam direction has been kept as simple as possible, there being no three-dimensional angulation of beams if it can be avoided, and the patient is either parallel or at right angles to the tube-axis. The

"pin-and-arc" device⁴, of Dobbie (1943) is used for all angular directions, while a very simple device⁵ is used for measuring the angle in space of the line joining two points on a patient. This takes the place of an emergent pointer, which, to be of any use, must be really rigid, a difficult mechanical problem at the relevant distances. Instead, the ingoing and outgoing points required are marked and their angle is measured directly and set on the tube.

X-ray photography at 1,000 kV on patients has served as a further check on arrangements, the films obtained being quite readable, and various bony markings just being visible. The films are slightly improved if 2 mm of lead is placed between the patient and the film. This tends to eliminate

⁴ The pin and arc device is, in effect, a large protractor, mounted on a stand with its centre removed and a retractable central pointer fitted. In the sketch (Fig. 6) the pointer is shown dotted at the centre of the protractor (point A). Rays are marked on the protractor panel at one-degree intervals radiating from A with zero vertical. The protractor is set in the correct position with the aid of a plumb bob attached at the right hand top corner. If it is required to direct the centre of a beam at a definite angle through a point inside a patient, the location of this point relative to a skin mark vertically above it being known, the device is used as follows. In the sketch the point to be aimed at is A, and it is say 9 cm below the skin mark B. The retractable protractor central point is raised 9 cm from its zero point, as indicated on the scale at C and the device is arranged so that the point is in contact with the skin mark B. The point A in the patient is then at the centre of all the protractor rays and, if the required angle is produced backwards onto the patient's skin, the central point of entry D of the x-ray beam is obtained. The depth (AD) of the point A from the central point of entry (D) of the beam is obtained by measuring the distance of D from a 30 cm arc E inscribed on the protractor from the centre A (AD = 30 cm less DE cm).

⁵ See Fig. 7. A hoop U shaped is fitted with a fixed point A and an adjustable pointer B on the other arm of the hoop adjustable so that the distance between A and B can be varied. On the hoop is fitted a protractor and plumb-bob C which reads 0 degrees when AB is vertical. If in the sketch the centre line of a beam has to enter at A and emerge at B on a patient's head the hoop points are adjusted to these points and the plumb-bob protractor reading is taken. This gives the angle required relative to the vertical. With the known divergence of a beam's edge the device can also be used if the required in and out positions of the beam edge are known.

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the scatter. The softer the scatter, the more it obliterates the detail, since the film-response is greater for the longer wavelengths. The film should be given 2 r. This technique has been particularly successful in carcinoma of the rectum, where a lead-loaded catheter in the rectum indicates the required features.

Conclusion

Even with the limitation that 200 kV techniques have been followed, significant differences in favour of million volt therapy have been found in the treatment of certain cancers, e.g., of maxilla and breast. There are striking differences in carcinoma of the rectum, where, in at least a third of the cases treated at one million volts, disappearance of the growth has occurred, while at 200 kV it is extremely rare for this type of cancer to show any response at all (Phillips, 1945).

Whether the improved clinical results in the types mentioned are directly due to the change in wavelength of the bombarding rays, or to the improved and simplified arrangements made possible by the physical properties of these rays, it is impossible to say, as the two effects cannot be separated. However, both the physical and clinical results are such that they lend support to the view that a further increase in voltage to the 5 to 10 million-volt range, is likely to give still better clinical results.

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PROTECTIVE METHODS IN RADIOLOGY

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Within a few years of the discovery of x-rays and radium, it had been established that the rays might be injurious to the health of the user. Many workers, through ignorance or indifference, developed burns and dermatitis, whilst some even lost their lives. In 1915, following a discussion on protection for x-ray workers, the Röntgen Society devised a set of suggestions regarding safety-measures, but during the next few years, due either to continued indifference of the workers or to a large increase in the amount of x-ray work undertaken by hospitals as a result of the war of 1914-18, there occurred a series of fatalities which greatly

disturbed public opinion. This led to the formation in 1921 of the British X-ray and Radium Protection Committee, which issued its preliminary report (Memorandum No. 1) in July, 1921. Other committees were set up at about the same time in other countries, e.g. the Safety Committee of the American Roentgen Ray Society, and the Commission du Radium, initiated by the Académie de Médecine.

The preliminary report of the British Committee not only indicated the way to ensure efficient protection against x-rays and radium gamma rays, but also drew attention to the necessity for suitable working conditions, condemning the practice of locating x-ray departments below ground-level, where natural lighting and ventilation were often inadequate. In Memorandum No. 2, issued by the committee in December, 1921, heads of x-ray departments of hospitals and other institutions were strongly advised to safeguard themselves and their staffs by insisting upon inspection of their departments, and of the various protective appliances, by the National Physical Laboratory.

Influence of Early Protection Recommendations on the Design of Sets

The British Committee insisted that a primary precaution in all x-ray work was to surround the x-ray tube as com-

pletely as possible with adequate protective material. As lead had a high absorptive value and was easily procurable and workable, it became the common practice to place the tubes in lead-lined boxes. These were, however, heavy and clumsy, and hindered the radiologists in their work. Accordingly, efforts were made to reduce the size and weight, without sacrificing any of the protection. These efforts led to the introduction of the so-called "self-protected" tube, of which the first example was produced by N V Philips' Gloeilampenfabrieken, Eindhoven, Holland (Bouwers, 1924). The main body of the tube was a chrome-iron cylinder, to which glass was sealed directly. Surrounding the cylinder was a lead sheath of sufficient thickness to absorb practically all the primary radiation from the target, with the exception of the useful x-ray beam.

Another unsatisfactory feature of early x-ray tubes and high-tension generators was the risk of electrical shock associated with their operation, since various parts of the equipment, working at several thousand volts, were often exposed. The British Committee suggested various precautionary measures, such as the introduction of earthed metal guards, the reduction of the high-tension conduit system to a minimum, and the mounting of the overhead conductors as high as possible, out of harm's way. These measures, though obvious, had not previously been generally adopted. A further advance was made in regard to high-tension protection by enclosing the tube and transformer in a single container and immersing them in oil. Generally speaking, such units were somewhat limited in regard to movement. In 1928, Bouwers designed shock-proof equipment which overcame this disadvantage. The tube was mounted in an earthed case and connected to the high-tension generator by means of shock-proof cables. This permitted the tube to be freely moved with respect to the generator. In recent years, particularly with super-voltage x-ray equipment, operating at voltages of 1 million volts or more, there has been a reversion to the scheme of enclosing the tube and generator in a single earthed metal tank. Reduction in the size of the apparatus has been achieved by using freon gas (Charlton, Westendorp, Dempster & Hotaling, 1939) or air (Trump, Van der Graaff & Cloud, 1940) under high pressure as the insulator.

Incidentally, the shielding of high-tension parts has led to improvements in another aspect of safeguarding the health of x-ray workers. It had early been observed that workers in x-ray departments complained of headaches and exhaustion, and of inflammatory conditions of the respiratory tract. These effects were attributed to nitrous fumes and ozone, generated by brush-discharge from sharp angles and points on the high-tension system. Subsequent experiments indicated that such effects as irritable cough, exhaustion, and blood-changes occurred if the ozone content of the air exceeded 0.5 mg per cm³. It was concluded that the effects observed in x-ray workers bore a great resemblance to the symptoms of ozone poisoning. Clearly, the introduction of shock-proof systems, with the consequent elimination of brush-discharge led to a further improvement in working conditions.

International Recommendations

At the first international congress of radiology, held in London in 1925, the question of international agreement on

the main principles of protection was discussed. Three years later, at the second international congress, held in Stockholm, the British Committee submitted its recommendations as a basis for agreement, and these were accepted with but few changes. The International Commission (1937) stated that its recommendations were designed to "deal only with the more essential matters involved, minor questions of detail being left to each country to elaborate. The question of seeking legal authorisation for such recommendations is left to each country to deal with as appears to it best."

Most countries have, up to now, preferred not to take legislative measures. In Great Britain, the safety measures recommended by the British X-ray and Radium Protection Committee (1943) receive the support of State Departments, such as the Ministry of Health and the Ministry of Labour and National Service, but those in charge of x-ray and radium departments are not compelled to adopt the safety measures nor to submit to inspection of their departments by the National Physical Laboratory. The recommendations have, however, in general, been followed by hospital authorities and factory managements, whilst the manufacturers of x-ray equipment have played an important part in the progressive improvement in conditions by designing equipment and departments in conformity with the committee's proposals. It may be mentioned that the Ministry of Labour and National Service issued an Order No. 703 on 1st April, 1942, regarding the health and safety-provisions for factory workers engaged in the use of radioactive luminous compounds. The Order does not, however, specify any tolerance-doses, and the inspections of luminizing departments which are carried out by the National Physical Laboratory on behalf of the Ministry are based upon the tolerance-doses suggested by the British Committee.

In the United States, safety recommendations are prepared by the Advisory Committee on X-ray and Radium Protection (U.S. Bureau of Standards, 1936, 1938).

Tolerance-doses for Ionizing Radiations

In toxicology, it is important to know what quantity of a particular poison can be tolerated without ill effects. The same position holds for ionizing radiations of all types, particularly those of a more penetrating character, since complete protection against them is, in the light of practical considerations, impossible. Before any protective schemes can be formulated on a sound basis, it is necessary to survey the various types of work undertaken with ionizing radiations and to have a complete knowledge of the ill effects which such radiations can produce. It is further necessary to know what quantity of each type of radiation a person can receive continuously without suffering any ill effects. This quantity is called the "tolerance dose". A subsequent task in formulating the scheme is to try to express the particular tolerance-dose in terms of a specifiable and reproducible biological standard, which in turn can, for preference, be measured in terms of a physical unit.

Of the present protective schemes it can be said that they are built on as sound a basis as existing knowledge of the ill effects of various radiations permits. As more evidence regarding blood-changes and genetic effects comes to light it may be necessary to amend the present estimated tolerance-doses and, consequently, the protective schemes themselves.

As regards the effects of x rays, clinical observations in

different countries led to various estimates of the tolerance-dose in terms of a somewhat uncertain surface biological effect, namely, the erythema. An average value of the figures published between 1925 and 1928 indicated that a person could tolerate a dose in 3 days corresponding to 1/1,000th of the amount of radiation required to produce an erythema. Meanwhile, work had been in progress with a view to establishing a physical unit for the measurement of quantities of x radiation. In 1928, the rontgen (r) was accepted internationally as the unit of x -ray quantity. Shortly before this, Kustner (1927) circulated a questionnaire to a number of institutions which were using deep-therapy apparatus (which, at the time, operated mainly at 200 kV), asking them to state the amount of radiation which produced an erythema. The average of the values given to Kustner, when translated into rontgens, was 600 r. The tolerance-dose thus corresponds to 600/1,000 rontgens in 3 days, or 0.2 r per day. This value is at present accepted as the basis of the recommendations of the International and British Committees. On the other hand, the American Advisory Committee on X-ray and Radium Protection take a value of 0.1 r per day as the tolerance-dose.

At the fifth international congress of radiology, held at Chicago in 1937, the definition of the rontgen was modified in such a way that it became a unit of gamma rays as well as of x rays. As regards the tolerance-dose of radium gamma rays, the early evidence indicated that it was likely to be of the same order of magnitude as that for x rays. Accordingly, we find that the current recommendations of the International and British Committees state that "the evidence at present available suggests that a person in normal health can tolerate with impunity exposure to x rays and radium gamma rays to an extent of about 0.2 international rontgen (r) per day or 1 r per week." In this respect, the American Advisory Committees have again chosen the lower tolerance-dose of 0.1 r per day.

Integral Dose and Tolerance

It will be seen that the present tolerance-doses are expressed in terms of the radiation falling upon the surface of the body. It has been emphasized by Mayneord (1940) and others that the total quantity of energy absorbed throughout the body of an irradiated person, or "integral dose" as it is called, is of considerable importance, both physically and clinically. For a given dosage-rate of radiation (expressed in rontgens per unit time) incident upon the surface of the body, the dosage-rates at various depths in the body will be greater the more penetrating the radiation. It follows, therefore, that the integral dose per unit surface-dose will depend on the quality of the radiation.

A suggested unit of integral dose is the gramme-rontgen, which is the quantity of energy absorbed when 1 rontgen of radiation is delivered to 1 gramme of air. Mayneord & Clarkson (1944) have drawn attention to the possible importance of integral dose in protection problems. For x rays excited at 40 kV (Siemens' "Doglas" therapy tube with no added filter, HVL¹ of 0.037 mm Cu), they find that the integral dose is of the order of 13,000 g/rontgens per rontgen measured on the patient's anterior surface. For x rays excited at 200 kV (Philips' therapy tube with 1.1 mm Cu added, HVL of 1.35 mm Cu), the value is about

46,000 g/rontgens per surface rontgen. Again, for 1,050 kV x rays (Metropolitan-Vickers' tube with filtration of 4.22 mm steel + 2.0 mm Pb + 2.0 mm Al, HVL of 10.4 mm Cu), the integral dose is 51,000 g/rontgens per surface rontgen, whilst for radium gamma rays (filter equivalent to 1.3 mm Pt, HVL of 16 mm Cu), the value is 59,000. This variation of the integral dose indicates that it may, in future, be necessary to express the tolerance-dose of x or gamma radiation in terms of the integral dose, measured in gramme-rontgens, rather than in terms of the surface-dose, measured in rontgens. Alternatively, since in practice it will be the surface-dose which is likely to be measured, it may be necessary to adopt different values of the tolerance dose, expressed in rontgens, for various qualities of radiation.

Genetic Effects²

At this stage it would be well to consider briefly the effects of ionizing radiations on genes and chromosomes and the influence which this knowledge may have in fixing limits to the amount of radiation which a person should be given. It is known that all types of ionizing radiations produce mutations, either of the individual genes or of the chromosomes, the rate of mutation being linearly proportional to the amount of radiation received. That is to say, no matter how small the given dose, there is a chance that a mutation may occur, although that chance will be very small. There is, therefore, no such thing as a tolerance-dose for genetic effects, if one interprets the phrase "tolerance dose" in its ordinary sense, namely, that the human body suffers no ill effects from such a dose. The genetic effects of radiation are accumulative and irreversible since, apparently, the mutation of a stable gene leads to another gene which is equally stable.

As the majority of hereditary changes are recessive in character, any inherited qualities do not become evident unless a mutated gene meets another like itself. Muller (1941) has calculated the chances of the meeting of two genes originating from independent mutations and has found that, on the average, at least 30, but more probably 100, generations would pass before a recessive abnormality of a seriously harmful nature would manifest itself by this process. There would thus be a "latent period" of 750 to 3,000 years. Muller has also calculated the chance of the meeting of two genes descended from the same original mutated gene, taking into account the degree of inbreeding. It is found that the latent period in this case is of the order of 5,000 years. It should be mentioned that spontaneous gene-mutations occur naturally, and that these may be produced by the effects of natural radioactivity.

Ignoring the ionization produced by the radioelements in the air, since the ions are largely due to alpha rays, which can have little effect on the body, it can be shown that the remaining ionization due to cosmic rays and to beta and gamma rays from radioelements in the air (Hevesy & Paneth, 1938) corresponds to a dosage rate of 2.2×10^{-8} r per sec, or to 0.002 r per day of 24 hours, or to 0.07 r per year. If all spontaneous mutations are caused by natural radiation—and this fact has not been established—then the natural mutation-rate can be said to correspond to the irradiation of the whole human race throughout past ages at the rate of 0.07 r per year, that is, to doses up to 5 r during the lifetime

¹ [Half value layer see footnote on p. 51.]

² [See also Catchside D. G., Genetic effects of radiations (BMB 800) in this number.—Ed.]

of each person. If then, from now on, only a fraction—for example, 1%—of the race is exposed to ionizing radiations either as workers or as patients, it seems logical to deduce that the natural mutation rate would at the most be only doubled even if each person in this minority received, on the average, 500 r in his lifetime.

In assessing the permissible dose on which to base future protection schemes, it will be necessary to know what fraction of the race is to be subjected to artificial radiation and what increase of the spontaneous mutation-rate is justifiable offsetting the degree of race-degeneration against the benefits bestowed by radiation. It does appear, however, that the suggestion made in an earlier paper by Muller (1939) that the dosage-rate should be reduced to 10^{-8} r per sec is much too cautious. Assuming a working week of 35 hours, and 48 working weeks per year, in conformity with the International and British Recommendations, Muller's figure corresponds to 0.06 r per year, which is slightly less than the natural radiation intensity. Hence, if the whole human race were exposed to an additional intensity of 10^{-8} r per sec, the mutation-rate would not be doubled.

The regulations of the Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege recommend that, for the genital organs, the daily dose should not exceed 0.025 r. This is one-tenth of the ordinary tolerance-dose accepted by the German X-ray Society. Jaeger & Zimmer (1941) considered that, as the number of workers using ionizing radiations in 1941 was still a relatively small proportion of the total population, even this value of 0.025 r per day represented a very cautious attitude.

Risks by Inhalation or Ingestion

We now turn to the consideration of other classes of radiation workers, namely, those who may suffer injury from radioactive materials which have been inhaled or ingested. As regards radon, the British X-ray and Radium Protection Committee recommend that "the radon of the air in laboratory, factory, workshop or other working quarters should not exceed a concentration of 10^{-10} curie per litre". As regards radium in the body, the Committee recommend that if, after the person has remained away from work for 48 hours, "radon then be found in a concentration of even 10^{-11} curie per litre, it is presumptive evidence of radium in the body and the operator should at once discontinue such work". In the National Bureau of Standards Handbook H 27 on the *Safe handling of luminous compound*, much lower tolerance-levels are advised, namely, "the radon concentration in the atmosphere of workrooms shall not exceed 10^{-11} curie per litre," and "no one shall be engaged as a dial painter who shows more than 0.1 microgram of deposited radium as revealed by the expired air test". It is stated that the latter figure corresponds to 10^{-12} curie of radon per litre of expired air. Assuming that the tidal respiratory volume per minute is 5 litres, it can be calculated that, if all the radon formed from 0.1 μ g of radium in the body appeared in the breath, the radon concentration of the expired air would be 2.5×10^{-11} curie per litre. The American figure of 10^{-11} curie per litre thus assumes that 40% of the radon is liberated. On the same basis, the British figure of 10^{-11} curie per litre corresponds to 1 μ g of radium in the body.

It must be mentioned, however, that the ratio of the liberated to the trapped radon varies considerably, not wholly in relation to the length of time during which the

radium has been deposited. In examining luminizers, the National Physical Laboratory therefore measures not only the exhaled radon but the gamma radiation from the disintegration-products of the trapped radon, as this is the only way in which to assess accurately the total amount of radium in the body.

There is much conflicting evidence regarding radium poisoning.

- i Evans (1943) reported that 7 persons carrying between 0.02 μ g and 0.5 μ g for 7 to 25 years revealed no clinical symptoms of chronic radium poisoning. Similar examples can be quoted from the results of tests made at the National Physical Laboratory on workers who have been engaged in luminizing for periods up to 30 years. In one case, a person who worked full time on actual luminizing for 30 years was found to have 0.7 μ g radium in her body, and there were no apparent ill effects.
- ii Opposed to the above is the evidence that fatalities have occurred when the radium burden was above 1.2 μ g.
- iii The "normal" amount of radium in the body is between 0.01 and 0.015 μ g. Expressing this in another way, Jones & Day (1945) calculate that the normal radium content of the body produces 0.025×10^7 ions per cm^3 of tissue per sec. For comparison purposes, they show that the radiation tolerance-dose of 1 r per week produces 2.69×10^7 ions per cm^3 per sec, whilst a radon concentration of 10^{-10} curie per litre in the atmosphere produces only 0.00008×10^7 ions per cm^3 per sec.
- iv The air of the Joachimstal mines contains from 20×10^{-10} to 60×10^{-10} curie of radon per litre, and occasionally as much as 200×10^{-10} curie per litre has been measured. Yet lung carcinoma among the miners is attributed to the dusts of arsenic and chromium, and not to the radon.

These conflicting facts indicate that much more evidence is required before the tolerance-doses for radium in the body and for radon and radium dust in the air of the workshop can be regarded as satisfactory.

Neutrons

There is another type of ionizing radiation—the neutron—against which adequate protection must be found. The neutron is approximately the same size as the proton (the nucleus of the hydrogen atom), and if the two collide, the neutron surrenders a large part of its energy to the proton, which recoils along a short path. Neutrons are thus effectively slowed down in hydrogenous material, such as tissue. The recoiling protons produce ions in the tissue, the ion-density along the proton track being far more intense than along the tracks of the electrons which are liberated in tissue by the passage of x or gamma rays.

Comparisons^a have been made of the biological effects of x rays, alpha rays, gamma rays and neutrons (Gray, Read & Poynter, 1943; Lasnitzki & Lea, 1940). These raise the problem of the measurement of neutron doses. Since neutrons liberate far more ions in tissue than in the same mass of air, it is not possible to measure neutron doses directly in

^a [See also Gray, L. H. Comparative studies of the biological effects of x rays, neutrons and other ionizing radiations (BMJ 199, 17 this number.—Ed.)]

rontgens The accepted practice is to define an "equivalent rontgen" of neutrons as the dose which produces the same number of ions per unit volume of tissue as a dose of 1 rontgen of x or gamma radiation. On this basis, it is found that the ratio of gamma-ray energy to the neutron energy required to produce a biological reaction varies from about 1.5 to 9, according to the reaction studied. On the other hand, the ratio of x -ray energy to gamma-ray energy shows much smaller variations, the average value being about 1.5. Clearly, further experiments will have to be made before a tolerance-dose for neutrons can be established.

Reference is made in Smyth's report on *Atomic energy* (1945), to the fact that the National Defense Research Committee of the United States set up a health group, one of whose tasks was to carry out research on the effects of radiations on persons engaged in the operations associated with the atomic pile. The results of the investigations of the group have not yet been announced, but doubtless the knowledge of radiation effects will have been greatly increased.

Elaboration of Protective Schemes

When the tolerance-dose for a particular type of radiation, say, x radiation, has been established and is measurable in terms of a physical unit, the subsequent procedure in determining the protection in any instance is to measure the dosage-rate of the radiation received at a specified point in terms of the unit adopted, to determine the transmission-values of the radiation through various thicknesses of various absorbing materials, and finally to calculate the thickness of the chosen absorbent which is required to reduce the transmitted radiation received at the point in question to the tolerance-dosage-rate.

It is well known that x rays and radium gamma rays are absorbed more effectively by lead than by any other common material. Hence lead or lead-impregnated materials, such as rubber and glass, have generally been used to secure protection. It is also customary to express the required protection in terms of lead and to determine the "lead-equivalents" of other absorbents.

When using x -ray equipment, steps must be taken to safeguard the operator against three types of radiation. In the first place, the tube itself must be protected in all directions other than that of the useful beam. Secondly, if the direct beam is pointed at the operator, as is often the case in screening a patient or object, a protective barrier must be placed in front of the operator. Thirdly, since all objects which are placed in the path of the direct beam scatter the radiation in all directions, the operator must be protected against this secondary radiation, either by means of a protective barrier or by relying on remoteness from the scattering objects.

Many papers have been published regarding the outputs of x -ray tubes operating under various exciting conditions. The results have been summarized by Kaye & Binks (1940) and Binks (1943) for exciting voltages up to 2 million volts. For tubes with "reflection" targets, that is, where the x radiation is emitted at right-angles to the electron stream, the outputs with a filtration of 0.1 mm copper are 2.1×10^{-4} (kV)^{1.8} r/min/mA at 1 metre over the range 75 to 200 kV, whilst with a filtration of 0.5 mm copper, the

outputs are 1.7×10^{-4} (kV)^{2.1} r/min/mA at 1 metre over the range 200 kV to 2 million volts. For tubes with "transmission" targets, that is, tubes in which the direction of the x -ray beam is a continuation of the electron stream, the x -ray outputs with a filtration of 0.5 mm copper are 2.1×10^{-6} (kV)^{2.6} r/min/mA at 1 metre over the range 600 kV to 2 million volts.

Turning to the corresponding question of the gamma ray outputs from known quantities of radium sealed in containers having a screenage equivalent to 0.5 mm platinum, the outputs can be calculated on the basis that the quantity of radiation received in 1 hour at 1 cm from a "point source" of 1 mg radium is about 8 rontgens. For distances other than 1 cm, the calculations are based on the inverse square law of radiation.

The preceding data on x -ray and gamma-ray outputs refer to the intensities of the direct beams. Far fewer measurements have been made of the intensities of scattered radiation (Binks, 1943), but one or two examples will illustrate the magnitude and importance of the intensities of scattered radiation encountered in practice. The dosage-rate at the side of a patient who is screened in the couch position is usually of the order of 100×10^{-5} r per sec. The daily tolerance-dose of 0.2 r would therefore be received in just over 3 minutes, which is about the time taken on one patient only. Hence the need for a protective screen on the side of the couch. In the case of x -ray therapy, the intensity of the scattered radiation at 1 metre to the side of a patient, who is exposed to 200 kV x rays from a tube run at 30 mA and having a filtration of 0.5 mm copper, is about 250×10^{-5} r per sec, corresponding to a dose of 0.2 r in 80 secs.

The absorption of direct and scattered x rays and gamma rays in various materials has been determined experimentally by workers in many countries. For direct x rays excited at voltages up to 5 million volts and for radium gamma rays, theoretical values have also been obtained (Kaye & Binks, 1940) for absorption in lead and for the lead equivalents of barium concrete.

From a knowledge of the outputs of x -ray tubes, working under various conditions of excitation, and from a knowledge of the degree of absorption of the rays in lead, it is a simple step to calculate the thicknesses of lead required to reduce the radiation at any point to the tolerance amount. Binks (1940) has prepared a simple nomogram, relating kilovoltage, milliamperage, distance and the amount of lead protection. By means of this, it is possible to find the amount of lead required to give adequate protection for any tube voltage between 200 kV and 3 million volts, for any tube current between 0.5 and 30 mA, and for any distance from the tube between 0.5 and 10 metres. A similar nomogram has been prepared (Binks, 1943) for the determination of lead protection against radium gamma rays. The corresponding protective thicknesses of other materials, such as brick, concrete and barium concrete, are also known (Kaye, Binks & Bell, 1938).

During the war there was a rapid increase in the number of workers engaged in luminizing instrument-dials and in the average quantity of radioactive luminous compound handled by each worker. As previously mentioned, the Ministry of Labour and National Service issued an Order in April, 1942, giving fairly detailed instructions to employers

and employees regarding the protective arrangements which are to be adopted in luminizing departments. The main features are

- i Protection against gamma radiation from the radium paint issued to each operator and against gamma radiation from the main stock of luminous compound possessed by the firm
- ii Protection of the exposed parts of the body against beta radiation. Each operator is to work behind a lead-glass screen, thus preventing beta radiation from the luminized object from reaching the face
- iii Local ventilation on each working bench, so as to remove radon and radium dust from the vicinity of the operator
- iv General ventilation of the workroom to remove radon and radium dust
- v Provision of special clothing for use in the workroom
- vi Periodical cleaning of bench-tops and equipment
- vii Personal hygiene

Similar proposals were put forward in America in the Bureau of Standards' Handbook H 27

Reference has already been made to the fact that neutrons can be decelerated in hydrogenous materials and are ultimately reduced to thermal velocities. The "thermal neutrons" are easily absorbed, in capture processes, by elements such as cadmium and boron which, in turn, become temporarily radioactive. In this phenomenon we find a method of protecting personnel against neutrons, produced by heavy particles accelerated by apparatus such as the cyclotron. Tanks of water up to 1 metre thick, or stacks of paraffin-wax blocks up to about 70 cm thick, are placed round the neutron source, most of the slow neutrons being absorbed by salts of cadmium or boron introduced into the water or wax. Any gamma radiation which is liberated is absorbed in a final sheet of lead.

Tests on Radiation Workers and Inspections of Radiological Departments

Since the introduction of the first report of the British X-ray and Radium Protection Committee, the National Physical Laboratory has continued to carry out inspections of radiological departments. Ionometric measurements are made at all points likely to be occupied by personnel and, if the dosage-rate at any point is found to be in excess of the tolerance-amount, methods of remedying the defective equipment or of improving the technique are suggested.

During the war, the Ministry of Health was disturbed at the increasing number of reported cases of low leucocyte-counts and, towards the end of 1942, consulted the Laboratory with a view to the establishment of a dosage-service. On the basis of many years' experience gained in the use of photographic films for monitoring the doses of radiation received by members of its own staff, the Laboratory organized a dosage film service on behalf of the Ministry. Later the service was extended to workers in Scotland and in Northern Ireland. In March, 1943, the Factory Department of the Ministry of Labour and National Service circularized industrial radiological departments, advising the managements to make use of the same film service.

Up to the present time, nearly 2,000 medical workers at about 550 hospitals and nearly 1,000 industrial workers at about 150 firms have been examined by the film method, many of the workers having been tested at three-monthly intervals, and a few continuously. The results show that over 70% of hospital x-ray staffs and over 90% of industrial x-ray staffs receive less than one-tenth of the weekly tolerance-dose. When a film test indicates that the wearer has received an excessive dose and the result has been confirmed in a repeat test, the Laboratory sends representatives to inspect the radiological department concerned. In some cases it is found that the equipment is defective, in others, that the technique is faulty. But it should be remarked that it has been found necessary to inspect only 9 hospital x-ray departments and only 12 industrial x-ray departments. There appears to be no need, therefore, for alarm regarding the low leucocyte-counts. Indeed, Britton (1943) found a low leucocyte-count in 29% of the 552 counts on 68 apparently-healthy nurses not exposed to radiation. He stated that this appeared to be a war-effect of unknown cause.

The films which are issued to radium workers are half covered with sheet lead 1 mm thick, which absorbs any beta radiation. The shielded half of the film thus records the gamma-ray dose, whereas the unshielded portion records both beta and gamma radiation. In the case of luminizers, it has been found that there is a large beta-ray effect, and subsequent inspections of many of the departments have revealed that most of the dose is due to contaminated benches and clothing. In the majority of cases, the total doses are now well below the tolerance level.

It seems possible to use the film technique for the measurement of neutrons which fall on the body. Fast neutrons would be slowed down in the tissue and would "evaporate" from the surface of the body with thermal velocities. If the film is covered with a thin foil of, say, cadmium, rhodium, or indium, which have a high-capture cross section, these elements would capture the neutrons, becoming radioactive and emitting ionization radiations which would blacken the film. The radioactivity should, preferably, be short-lived, so that there would be no need to take into account the lapse of time between the initial irradiation of the film and the photographic development.

The inspections of luminizing departments also include tests of the radon concentration of the air of the workrooms, and tests of the radium in the bodies of luminizers, part of the radium being assessed by means of the alpha rays from the radon contained in the exhaled air and part by means of the gamma rays from the subsequent disintegration-products of the radon trapped in the body. Similar tests have been carried out by Jones & Day (1945).

It will be apparent from the foregoing review that, whilst there is much to be learned about the tolerance-doses for various types of ionizing radiation, and whilst there is an ever-growing number of radiological workers using an ever-widening range of man-made radiations, sufficient experience has already been gained to be able to tackle the new protection problems with high hopes of evolving effective safety measures.

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809

EXCHANGE OF DIAGRAMS AND DATA BETWEEN RADIOTHERAPY CENTRES

A scheme developed by the Association of Hospital Physicists

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Often graphs and diagrams which appear in the literature are too small to be useful, and many workers would like to have full-size copies of the originals. Also, institutions accumulate diagrams, nomograms and data (some of the latter the result of laborious computation, e.g. Klein-Nishina coefficients) for their own use, which are not published, but would be very useful to others if an interchange of copies could be arranged. A graph, or table of data, often represents in a condensed form the results of a great deal of work. The Association of Hospital Physicists has therefore developed an organisation by which this exchange can be effected.

The Association has collected lists of diagrams, data, etc., which institutions are prepared to lend for reproduction, and has classified them in a catalogue of 213 such items. A person desiring any copies of these may apply to the secretary of the Diagrams and Data Sub-committee for them. He requests its loan from the owner, obtains a positive and negative copy from a firm which specializes in such reproduction, returns the original to its owner, and sends the copy to the person who requested it. The negative is retained by the secretary for future use. It is not therefore necessary to trouble an owner for the loan of a diagram, etc., on a second occasion, which itself is a gain to those who receive frequent requests for information.

At the present time many books, especially those of foreign origin, are difficult to obtain. The catalogue therefore contains a list of such books which the owners are willing to lend for limited periods. The demand for authors' reprints often exceeds the supply. A start has therefore been made in the collection of negatives of such reprints from which copies can be produced.

The material of the catalogue is arranged in four columns. The first gives a classification-number for each item, the second a description of each item, the third a reference number which, with a key, indicates from which institution the item originated, and the fourth gives the dimensions in inches. The classification numbers are each divided into blocks of digits by decimal points. The last block (to the right) gives in all cases the number of the item in the smallest sub-group. The first block (to the left) gives the number of the main classification-group. Further blocks give the numbers of sub- and sub-sub-groups. The classification, together with the number of items which the catalogue contains in each group, is as follows.

1 X RAYS

- | | | |
|-----|---|----|
| 1 1 | Isodose curves other than those contained in Professor Mayneord's list (1943) | 81 |
| 1 2 | Wedge field and other non standard isodose curves | 3 |
| 1 3 | Volume dose graphs and data | 4 |
| 1 4 | Physical data relating solely to x radiation | 4 |
| 1 5 | Miscellaneous | — |

2 RADIUM

- | | | |
|-------|--|----|
| 2 1 | Radium bomb isodose curves | 16 |
| 2 2 | Isodose curves and rules, graphs etc for dose calculation for radium sources — | 17 |
| 2 2 1 | Linear sources | 2 |
| 2 2 2 | Ring source | 9 |
| 2 2 3 | Disc and other plane sources | 5 |
| 2 2 4 | Volume distributions | 5 |
| 2 2 5 | Miscellaneous sources | 5 |
| 2 3 | Physical data relating solely to radium and gamma radiation (tabulated mathematical functions and associated diagrams are given under the main classification MATHEMATICAL DATA) | 1 |
| 2 4 | Miscellaneous | 2 |

3 PHYSICAL DATA

- | | | |
|-------|---|----|
| 3 1 | Scattering and absorption data for radiation in general | |
| 3 1 1 | Data relating to scattered radiation based on the Klein-Nishina and Compton formulae | 11 |
| 3 1 2 | Photo-electric absorption coefficients | 4 |
| 3 1 3 | Miscellaneous absorption and transmission data | 7 |
| 3 2 | Energy absorption, properties of ionizing particles, distribution of ion pairs | 4 |
| 3 3 | Data of biophysical interest (tabulated mathematical functions and associated diagrams are given under the main classification MATHEMATICAL DATA) | 2 |
| 3 4 | Miscellaneous | 2 |

4 MATHEMATICAL DATA

5

5 MACHINE DRAWINGS

- | | | |
|-----|---------------------------------------|----|
| 5 1 | Ionization chambers and electroscopes | 5 |
| 5 2 | X-ray apparatus | 5 |
| 5 3 | Radium apparatus | 4 |
| 5 4 | Circuit diagrams | 5 |
| 5 5 | Miscellaneous | 10 |

6 BOOKS

A number of isodose curves, which are not contained in the catalogue, can be obtained from the secretary of the Royal Cancer Hospital (Free), Fulham Road, London, S W 3 (Mayneord, 1943).

All the classification numbers are preceded by the letter A, which shows that the items are contained in Catalogue A of December, 1944. It is intended to issue other catalogues

B, C, ... from time to time containing matter which has accumulated in intervening periods. It is hoped to issue Catalogue B in the near future, containing some 200 new items. The catalogue, and in most cases the diagrams, etc. give the name of the institution or person from which each item originates. This affords the same guarantee of accuracy of unpublished data as must be relied on when published data are used, except, of course, that it has not been scrutinized by the reading public.

It is intended that the scheme shall be financially just self-supporting. Accordingly a charge is made sufficient to meet the cost associated with each order, with a small addition towards overhead expenses. The charges will be adjusted from time to time to balance income and expenditure. They vary with the size of diagram or extent of typewritten data, but so far the average cost per item has been about 4s 6d [£0 22s]. Copies of Catalogue A can be obtained from the honorary secretary at a cost of 5s [£0 25s] each.

During the first 18 months of operation of the scheme, over 200 items have been supplied to some 20 different institutions. Twenty-seven have been sent to Canada and

the USA. The secretary now possesses 118 negatives of diagrams and copies of data, so that copies of these can be supplied without the delay of borrowing the originals.

The scheme is obviously capable of geographical extension. Copies of Catalogue A have gone to Australia, Canada, New Zealand and the USA. It is hoped that similar schemes will be organized in other parts of the world, with co-operation between the groups. Perhaps it will help, in a small way, in the reconstruction of radiotherapy in the devastated parts of Europe, since useful diagrams and data of general applicability can quickly be supplied. In Britain, the scheme has been of considerable service to new radiotherapy centres, and to physicists appointed to hospitals for the first time. A study of the items subscribed to the catalogue by different centres shows that each places emphasis on a rather different aspect of the work. The scheme facilitates the pooling of these somewhat divergent activities, so that all can benefit from the special interests of each.

REFERENCE

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810 BOOKS

(The prices quoted are those which obtain within the United Kingdom. Editors of overseas medical journals who wish to review publications of which notices appear below are invited to apply to the Editor for review copies, of which a few are sometimes available. Orders for any of the publications mentioned below may be sent to the Editor if there are difficulties in obtaining them locally. Publications may be referred to by the numbers given at the left of each item, e.g. Book 186. It should be noted that supplies of all publications are limited and there can be no certainty that publications ordered or requested for review will be available. Publications are classified according to the Universal Decimal Classification and the classification number of each publication is given at the right.)

TRAUMATIC SURGERY

186 Acute Injuries of the Head

617 51

G. F. Rowbotham. SECOND EDITION. EDINBURGH, E. & S. LIVINGSTONE LTD., 1945. Pp. 424. 201 ILLUSTRATIONS. 25 x 17 cm. £1 10s. [£1 5s]

The publication of a second edition of this work within two years indicates its well-deserved popularity, and the author is to be congratulated for his industry during a period of great stress. There is an almost inevitable tendency for text-books to grow, and this edition is about one half larger than the earlier one. It deals very thoroughly with its subject and is of a convenient size. Further room can be gained in the future by omitting unimportant material, such as the illustrations of the staff and country-side of a rehabilitation centre, the introductory remarks on pathology and general descriptions of air-raid casualties. One would like to see more precise information about the use and value of penicillin rather than a whole paragraph concerning the accidental discovery of its potentialities. The standard of paper, printing and illustrations is excellent, though in some instances the details of x rays have seemingly suffered in reproduction.

The diagnosis of closed injuries is a difficult but most attractive subject. The chapter dealing with this has been considerably enlarged—well justified by its importance—and it is probably the best in the book. Illustrative case-records have been inserted, which should prove helpful, but they might have been pruned more vigorously. Fractures of the skull are now dealt with in a separate chapter, and careful consideration is given to the importance or otherwise of closed fractures.

Headache and dizziness, the two most frequent and troublesome post-traumatic symptoms, are dealt with in great detail, and a valiant effort is made to analyse the possible causes of headache in the light of present knowledge. Although unfortunately there is still much hypothesis in this field, it is noteworthy that the author believes in a physical basis for most post-traumatic headaches, even if there be psychogenic factors as well. Neurosis and psychosis after head injury are discussed, but traumatic intellectual impairment is dismissed somewhat cursorily. One hopes that this omission will be remedied in the future. Intellectual deficit forms one of the reliable criteria of the degree of brain damage and upon its correct assessment largely depends the person's successful replacement in industry. It is especially in this field that the neurological surgeon looks to his colleagues the neurologist and psychiatrist, for help and guidance. In the diagnosis of the sequelae the author gives the impression that the separation of neurotic from other symptoms is practicable. But this differentiation is so difficult and of such doubtful value, that neuro-psychiatrists are now disinclined to classify the symptoms of these cases as either organic or psychogenic, but accept that both may operate—one or the other possibly predominating—in a given case of brain injury.

The activities of a rehabilitation centre, and post-traumatic epilepsy are each given a chapter, it would be valuable to include long-term results of the surgical treatment of epilepsy. In the first edition, the final results of head injuries occupied only a page and a half, but these have now been expanded to fourteen, this provides a most useful analysis of figures from various sources—including the author's experiences. There is also information about the prognosis of focal sequelae, such as defective vision and hearing and the book concludes with an entirely new chapter on birth-injuries.

187 **Technique in Trauma: Planned Timing in the Treatment of Wounds including Burns**

F B Gird & F D Ackman LONDON WILLIAM HEINEMANN (MEDICAL BOOKS) LTD 1945 68 PAGES 17 ILLUSTRATIONS AND 3 COLOURED PLATES 25 x 18 cm 15s [£0 75]

This book, from the Montreal General Hospital and McGill University, consists of three articles published in the *Annals of Surgery*. Additional text and an exhaustive commentary have been appended.

The first article describes the principles upon which the method is based and the practical details of their application to the burned patient. The second, published a year later, reviews 100 cases treated along these lines. It includes case-histories and very frank and critical commentaries on the management of many of the cases. It also includes, on page 33, a number of modifications of the original plan as outlined in the first article. It is important that the reader's attention should be drawn to this, since one of the changes made is the abandonment of escharotics for body burns which are recommended in the first article. This is particularly important, since a tabulated summary of treatment recommending escharotics and "intended to be a ready reference to all doctors and nurses" (page 21), is included in the first article. A revised table, from which they have been omitted, is included in the second article. The third article describes the application of the authors' method of treatment to wounds and infected surfaces.

The method advocated is designed to anticipate the commonly-occurring complications of burns and wounds. In consequence, stress is laid on the importance of timing all therapeutic measures correctly—"of doing the right thing at the right time." In burns a system of general and local treatment is elaborated to anticipate shock, toxæmia, infection and disability from slow healing. Shock is combated by the usual methods. The burned surfaces are gently cleaned without an anaesthetic. They are then covered with an occlusive pressure dressing and immobilized in a plaster cast. The pressure-dressing consists of "sulpha-mesh" (tulle gras), backed with several layers of gauze generously impregnated with sulphathiazole emulsion, and covered with a thick cotton-wool pack. The use of a water-in-oil emulsion is advocated since the molecular solubility of the sulphathiazole in the emulsion is 5.5% compared with a solubility in water alone of only 0.07%. The emulsion yields its content of sulphathiazole at a slow, even rate. Superficial burns are dressed after a week. Deep burns are dressed in 10-14 days under anaesthesia. Debridement and grafting are carried out at the same time. This method of delayed debridement and "delayed primary grafting" are the only differences from the routine treatment of burns in Britain. In Britain, the sloughs are usually allowed to separate spontaneously and the grafts are applied afterwards (21st day approximately). The extent and depth of the burns of modern warfare probably explain these differences.

Wounds are treated on the same general principles. The importance of adequate therapy for shock and careful débridement are stressed. Primary suture and primary grafting are recommended for suitable cases treated within six hours of injury. For others, "sulpha-mesh," sulphathiazole emulsion, occlusive pressure-dressings and plaster casts are used. Delayed primary suture and delayed primary grafting are undertaken at the first or second dressings, 7 and 14 days later. Secondary suture or secondary grafting are undertaken as soon as possible for those cases not suitable for immediate or delayed primary closure. The parenteral administration of sulphonamide is not recommended unless a systemic complication such as pneumonia supervenes. There is no mention of penicillin.

The book illustrates what can be achieved by team-work. Without the stimulus of large numbers of war casualties, and thousands of miles from a theatre of operations, the authors have evolved a method of treatment identical in principle and similar in detail to that in use in Britain to-day. The reasoned

approach to the many problems involved and the carefully controlled clinical application of the solutions to these problems are exemplary and reflect great credit on the staff of the Montreal General Hospital.

AN INTRODUCTION TO ANATOMY

611

188 **The Tissues of the Body** An Introduction to the Study of Anatomy

W E Le Gros Clark SECOND EDITION OXFORD CLARENDON PRESS 1945 xi + 388 PAGES, 120 ILLUSTRATIONS 24 x 16 cm £1 1s [£1 05]

The second edition of this book makes a timely appearance. First published in 1939, the impact of total war, whilst it did not prevent its recognition as a book of outstanding merit, did preclude its widespread adoption. Apart from the fact that opportunity has been taken to bring the material up to date and to improve the illustrations without any considerable expansion of the text, the book remains much the same as in the first edition.

For many years the study of anatomy has been predominantly the study of the end-products of tissue organization. Tradition and the limitations of the time-table have given teachers and text-book writers alike little opportunity to deal with the structural organization of the body as a dynamic process. This book fulfils this long-felt want. Commencing with a study of the cell and a short account of the development of the tissues in the embryo, the author proceeds to discuss connective tissues, cartilage, bone, muscle, the tissues of the joints, blood, blood vessels, lymphatic tissues, mucous membranes and glands, skin and the tissues of the nervous system. The text is lucid and illustrated with 120 diagrams. Although the book has been written as an introduction to the study of anatomy the author has taken the opportunity to indicate the lines upon which our more recent knowledge has been obtained. In this he is to be congratulated. The text remains concise and clear and yet stimulating and dynamic. It is outstanding in that it bridges the gap between the physiological histologist and the micro-anatomist. This book merits a place in the library of every student of biology.

The letterpress, illustrations and format are worthy of the text.

DENTAL SURGERY

616 314-089

189 **Essentials of Surgery for Dental Students**

J Cosbie Ross EDINBURGH E & S LIVINGSTONE LTD 1945 284 PAGES, 194 ILLUSTRATIONS 22 x 14 cm £1

This book wins golden opinions from all students who have handled it and is widely regarded as the best book yet produced in its own special field. In a text-book of this type it is inevitably difficult to decide what to include and the depths to which the various subjects are to be treated.

The handling has in general been good. The illustrations are many and in the main excellent. One's impression is that often the black and white photographs convey the point better than do some of the colour plates. The colour plate of Hutchinson's teeth would have been better inverted, since it is the upper jaw that is represented.

Inevitably slight differences in outlook are liable as between the general and the dental surgeon. Perhaps this accounts for the preference expressed for open ether as the anaesthetic in opening an alveolar abscess, instead of nitrous oxide as preferred by the dental surgeon. The author is confused in his discussion of the treatment of dental cyst, since in the Pertsch operation the lining is left, not removed.

A more serious point of difference arises in the chapter dealing with cleft palates, wherein one finds the statement "The most favourable period for operation [for cleft-palate repair] lies between eighteen and twenty-four months." From the stand-

¹[On the use of the word *débridement* see footnote to *BMB* 703 and also *Bull War Med*, 1945, 5, 422.—Ed.]

²[British methods are comprehensively summarized by F H K. Green in *BMB* 690.—Ed.]

point of minimal speech defects, it would seem desirable to effect repair before the child begins to speak, nearer therefore to one year than two years of age.

Another minor criticism arises under the heading of "Fractures of the mandible," wherein it is suggested that fracture of the neck of the condyle is rare. One's own experience indicates that this condition is more frequent than is suggested, but that it is not infrequently missed by the general surgeon. One would have expected a brief statement on the use of bone-chips or -paste, as described by Mowlem and other workers, under the heading of bone grafts, rather than the method described. As to the stigma of a syphilitic origin for the cusp of Carabelli, this is now widely regarded as untrue.

Such points of criticism will almost certainly be dealt with when a second edition appears.

This review would not be complete without expressing a word of appreciation of the effort of the publisher.

Chapter headings (i) clinical examination, (ii) the lips, (iii) the tongue, (iv) the buccal cavity, (v) the salivary glands, (vi) hare-lip and cleft palate, (vii) alveolar abscess, (viii) osteomyelitis and necrosis of the jaw, (ix) tumours of the jaw of dental origin, (x) tumours of the jaw of non-dental origin, (xi) the temporomandibular joint, (xii) fracture of the jaw, (xiii) wounds and their treatment, (xiv) plastic surgery and deformities of the jaw, (xv) lesions of the face and scalp, (xvi) neuralgia and other cranial nerve lesions, (xvii) the cervical lymphatic glands, (xviii) non glandular swelling of the neck, (xix) the thyroid gland, (xx) syphilis, (xxi) shock, haemorrhage, gangrene, and embolism, (xxii) radium therapy, (xxiii) diseases of the nose, pharynx, larynx, ear and eye.

616 314-089 28

190 Mechanical Dentistry. A Practical Treatise on the Construction of the various kinds of Artificial Dentures

BASED ON THE EIGHTH EDITION OF CHARLES HUNTER'S WORK OF THE SAME TITLE, RE-EDITED BY E. Samson. LONDON: TECHNICAL PRESS LTD., 1945. 208 PAGES. 117 ILLUSTRATIONS. 22 x 14 cm. 15s. [£0.75]

As the foreword to this book indicates, it is, in effect, a re-editing of the eighth edition of Charles Hunter's work of the same title. It is a pity that evidence of this fact is not to be found on the dust cover, since it is clear from a reading of the text that the personal contribution made by Mr. Samson is a small one.

In view of Mr. Samson's widespread comments on many aspects of dentistry one approached with especial interest the review of this book. It was therefore a particular disappointment to find so little in it that one can commend. The only justification for its publication would seem to be in consequence of the possible historical value of much of its contents.

It is important that foreign readers should not consider the book as representing the present state of mechanical dentistry in Britain. In the chapter dealing with impression-materials reference is made, in a footnote, to zelex, "as perfect in results and far easier to manipulate than dentocoll." No comment is made as to the shortcomings of the alginate materials as evidenced by the adverse comments of many commercial laboratories. The author says that in casting the model "we should have what is called a 'hard model'—the only way known is by mixing plaster thick or using one of the artificial stones." This illustrates the type of superficial comment on present-day procedures. In the chapter on "Gold for swaged plates" one finds a picture of a brick-built draught-furnace for gold, and, in keeping with the truly Victorian sentiment so characteristic of most of the book, one finds complete directions for alloying gold, using as the starting point that rare, nay, virtually unknown, coin, the English golden sovereign. Having dealt with the matter very fully in a page and a half, the editorial footnote laconically remarks that the use of the English sovereign for melting is now illegal.

A chapter on ceramics is strangely reminiscent of the literature on this subject put forward by the Amalgamated Dental Company.

Considerations of space prevent one dealing with all the limitations of the text, but it is obvious that any text book

published in 1945 that omits all reference to acrylic resins and cast stainless steels can command little interest for those concerned with recent developments.

Such minor errors as the atomic weight of silver, 108, the freezing point of mercury, 37.9° F, do not seem to have troubled the proof reader. Chapter 17, under the heading, "Properties of metals, specific gravity, etc.," contains the solemn statement, "Fixed loils expand 1/12, that is, 12 measures become 13"!

In the reviewer's opinion, the book is, from the standpoint of present-day knowledge, a lamentable failure.

A MEDICAL REFERENCE BOOK

614 (058)

191 Health and Social Welfare, 1945-1946

ADVISORY EDITOR, Rt Hon Lord Horder, LONDON: TODD PUBLISHING COMPANY LTD. 1945. 519 PAGES. 22 x 14 cm. £1 1s. [£1.05]

The second annual issue of this yearbook more than fulfils the promise of its predecessor. All sections have been enlarged and the present volume is more than twice the size of the first. Its 520 pages contain an extraordinary amount of up-to-date information concerning all aspects of health and social welfare throughout the world.

Section 1 contains 30 articles by recognized authorities on a wide range of medical and medico-social topics. Of special interest at the present time are those by Sir John Boyd Orr on "Nutrition and national health," by Hilde Fitzgerald on "A national health service," and by Professor F. A. E. Crew on "Social medicine." Miss Dorothy Manchée's article on the hospital almoner admirably fills a gap to which we drew attention in our review of the first issue of this annual. Section 2 is a survey of health legislation and policy. Section 3, one of the most useful in the book, contains official directories of governmental and other official bodies concerned with health, both at home and abroad. Section 4 consists of official statements setting out the scope and functions of ministries and government departments, and of such bodies as the Charity Commission, the General Medical Council, and the General Register Office. Section 5 gives similar information regarding a large number of non-governmental bodies and institutions. Section 6 deals with officially-appointed committees and contains much useful information which is not to be obtained from any other printed source. Section 7 consists of an article on "Careers in professions associated with health and social welfare," by Miss Isabella Williams. Section 8 is a directory of organizations interested in health and social welfare, it is comprehensive and gives full addresses and telephone numbers. Section 9 consists of statistics and tables, and will save many from the sloughs of the official returns. Section 10 lists books, periodicals and films. Section 11, a "Who's who in health and social welfare," is the weakest in the book. Many of those listed, although eminent enough in their respective spheres, appear to have no special connection with health or social welfare. An excellent index has now been provided, but this feature might be still further improved if the principal references under some of the longer entries were indicated in heavy type.

An invaluable reference book such as this needs no extraneous adornment, but many of its users will nevertheless be grateful for the striking photograph of the Minister of Health and the lifelike caricatures by Sallon which are provided.

PHYSIOTHERAPY

615 82

192 Physical Treatment by Movement, Manipulation and Massage

JAMES B. MERRILL. FIFTH EDITION. LONDON: J. & A. CHURCHILL LTD. 1945. 512 PAGES. 288 ILLUSTRATIONS. 22 x 14 cm. £1 10s. [£1.5]

The first appearance of this book in 1917 marked a great step forward towards the practice of rational physiotherapy. The ground was cleared for critical examination of the indications for and against the employment of physical measures, the

physiological basis for treatment by exercises and manual methods was set out, and the field of massage and manipulative technique was comprehensively surveyed. This volume rapidly became the stand-by of the enquiring physiotherapist and interested medical man. But succeeding editions have proved disappointing, for the author has allowed the book to fall increasingly behind the times. The results of recent research in the field of physical medicine have not been reflected by corresponding changes in the text. On the one hand, the value of many of the methods advocated has become so universally recognized that they are incorporated in the everyday practice of rehabilitation. On the other, methods based on ideas no longer held are still included in the text, though, in fact, in large part rejected by the medical profession (e.g. massage for fractures). The rigidity resulting from lack of revision leads to the curious situation whereby excellent material and abandoned concepts are presented throughout with equal emphasis.

The first hundred pages are devoted to consideration of massage, relaxed passive movements and exercises. This part of the book is not important. The value of exercises is in no doubt and several established treatises deal with it fully. Relaxed movements have been all but abandoned, and massage is nowadays seldom ordered for the conditions under discussion. Moreover, Dr. Mennell permits himself to address the physiotherapist in a prose style mingling prolixity, exhortation and warnings in a manner both confusing to her and out of place in a scientific work.

The author then passes on to forced movement. Here he remains master of his subject and the matter presented is of outstanding interest. The account of the range of movement at various joints is excellent, well-chosen skiagrams illuminate the points made. The most suitable grip for each manipulation is described in the text and illustrated by clear photographs. This is the most valuable part of the book, one would wish that it had been expanded.

Fifty pages are set aside to backache and sciatica. A system of examination is suggested, but the significance of the various possible findings is presented in a confusing way. This is perhaps inevitable, for the author regards backache and sciatica as commonly resulting from sacro-iliac-joint lesions and contracture of the ilio-tibial band. The research carried out over the past ten years on protrusion of a low lumbar intervertebral disc is wholly ignored. Thus, no coherent picture may be expected to emerge when tests are described for joint and fascial lesions with which the symptoms under discussion are now known to be unconnected.

This pioneer book on physiotherapy should be read in a discriminating spirit by all students of the subject. There is much that is good and true in it, other parts have not stood the test of time. Nevertheless, no text-book has yet appeared to take its place, hence one may be permitted to hope that it will be Dr. Mennell himself, in a future edition, who will so revise, curtail and expand the contents that they once more provide guidance on to-day's problems in the field of physiotherapy.

NEW EDITIONS

193 The Medical Annual, 1945

61 (058)

EDITED BY *Sir Henry Tidy & A. Rendle Short* BRISTOL, JOHN WRIGHT AND SONS LTD., 1945. 410 PAGES, 47 PLATES. 61 ILLUSTRATIONS. 21 x 14 cm. £1 5s. [£1 25]

Several new subjects are included in this latest issue of the *Medical Annual*. A review of Vital Statistics is contributed by Dr. Percy Stocks. Primary Atypical Pneumonia receives recognition with a chapter written by Col. W. S. Middleton, of the U.S. Army Medical Corps. Yellow Fever Control is discussed in a special article by Major-General L. T. Poole and Major J. W. Howie. Major-General Poole and Lieut.-Colonel H. J. Bensted also review fully the subject of Scrub Typhus (tsutsugamushi disease). The serious proportions attained by this disease during the jungle warfare in the Far East gave opportunities for its intensive study.¹

A special article on the indications and contra-indications for penicillin treatment is written by J. S. Jeffrey, and is particularly useful now that supplies of this substance are becoming generally available. The war experiences of many of the contributors are reflected in this volume, which continues to provide a concise review of recent progress in medical treatment, particularly valuable for the general practitioner.

194 Synopsis of Obstetrics and Gynaecology 618 (02)

Aleck W. Bourne NINTH EDITION BRISTOL, JOHN WRIGHT AND SONS, 1945. 500 PAGES, 168 ILLUSTRATIONS. 18 x 13 cm. £1 1s. [£1 05]

This is a useful handbook for students preparing for qualifying midwifery and gynaecology examinations. It sets forth the principal points of obstetrics and gynaecology in a simple and concise manner and is intended to be used as a supplement to, rather than a substitute for, the usual textbooks. This edition has been very thoroughly revised, and mastery of its contents by the student should enable him to satisfy the demands of the examiners.

195 Materia Medica. Pharmacy, Pharmacology and Therapeutics 615 (02)

Sir William Hale-White 26th EDITION, REVISED BY *A. H. Douthwaite* LONDON, J. & A. CHURCHILL LTD., 1944. x + 534 PAGES. 18 x 13 cm. 14s. [£0 7]

New editions of "Hale-White" appear with a frequency which is embarrassing to the reviewer, and it is difficult to find anything to add to what has previously been written about it. The book has achieved 26 editions in 52 years and is well known to all medical practitioners and senior students in Britain. It gives an account of the composition, dose, action and indications for all therapeutically important drugs in use at the present time, and in this new edition mention is made of the most recently introduced sulphonamides, new anticoagulants, hormones and penicillin. The section dealing with the sex hormones has been revised by Dr. P. M. F. Bishop. Enlargement of the index, a feature of the two previous editions, has been continued in order to supply more therapeutic references, we hope that the unhappy term "tubercular vaccines" will be omitted in the next edition.

196 The Diagnosis of Nervous Diseases 616 8 (02)

Sir James Purves-Stewart NINTH EDITION LONDON EDWARD ARNOLD & CO. 1945. viii + 880 PAGES, 358 ILLUSTRATIONS. 1 COLOURED PLATE. 22 x 14 cm. £2.

Chapter headings (i-ii) physiological anatomy, (iii) method of case-taking, (iv) delirium, (v) coma, (vi) convulsive phenomena, (vii) involuntary movements, (viii) aphasia, (ix) disorders of articulation, (x-xi) cranial nerves, (xii) pain and other abnormal subjective sensations, (xiii) abnormalities of sensation: hyperaesthesia, paraesthesia, anaesthesia, (xiv) organic motor paralysis of upper neurone type, (xv) organic motor paralysis of lower neurone type, (xvi) recurrent and transient palsies, (xvii) inco-ordination, (xviii) postures and gaits, (xix) tropho-neuroses, (xx) reflexes, (xxi) affections of the vegetative nervous system, (xxii) the psycho-neuroses, (xxiii) electro-diagnosis and electro-prognosis, (xxiv) the cerebro-spinal fluid, (xxv) disorders of sleep, (xxvi) intra-cranial tumours.

This is a new edition of a well-known book which first appeared forty years ago, revised in the light of the rapid advances made in neurology during recent years.

In his preface the author, who is consulting physician to the Westminster Hospital, the West End Hospital for Nervous Diseases, and the Royal National Orthopaedic Hospital, relates how, returning from America primed with fresh references and new illustrations, he was unfortunate enough to lose by enemy action all this material and his manuscripts of the new edition. We had hoped that in this edition some of the older illustrations would have been replaced by more modern pictures. Nevertheless, there are some new illustrations, and there will be a warm welcome for this new edition of an established favourite.

¹ [See *BMB* 781 for a report of work on this disease—ED.]

197 Handbook of Diagnosis and Treatment of Venereal Diseases 616 957

A. E. W. McLachlan SECOND EDITION EDINBURGH,
E. & S. LIVINGSTONE LTD, 1945 371 PAGES, 159 ILLUSTRATIONS (20 IN COLOUR) 19 x 13 cm 15s [£0 75]

The call for a second edition within eighteen months¹ confirms the success of this textbook in providing elementary instruction for the student and concise facts for the practitioner. The notable feature of tabulating the differential diagnosis of venereal lesions and other conditions commonly mistaken for them remains unaltered. The fuller consideration of the interpretation of the routine serological tests for syphilis, the intensive arsenotherapy of early syphilis now more widely applicable, and the use of penicillin for both gonorrhoea and syphilis, has improved the value of this second edition.

Few will quarrel with the advice that patients with gonorrhoea should be hospitalized for 24 hours when receiving penicillin but for various reasons, including the scarcity of nurses and hospital staff, this Utopia is seldom attainable in practice, the majority perforce are treated, adequately and with a minimum of inconvenience and financial loss, as out-patients. The author believes a total dosage of 100,000 units of penicillin in five equal intramuscular injections of 20,000 units at three hourly intervals to be sufficient to cure most cases of acute gonorrhoea. If combined with sulphadiazine or sulphathiazole, this may be so, but for two reasons, many prefer the higher dosage of 150,000 units in five injections of 30,000 units at two hourly intervals.

¹ [For review of first edition, see *BMB* 387/36.]

relapses are fewer and the cure-rate is higher, and as an out-patient, only one working day is required. This obviates hospitalization and patients' embarrassment at having to explain unexpected absence from home for a night. Indeed, to assure security, recent experience suggests that a still higher dosage of 200,000 units is advisable in most cases. The difficult question of the criteria of cure in gonorrhoea, especially in this new era of sulphonamide and penicillin therapy, is hardly elaborated enough for a subject of such crucial importance to both patient and practitioner.

The chapters on the clinical aspects of syphilis in all its stages, including late generalized syphilis, lesions of bones, joints, muscles, viscera, cardiovascular and neurosyphilis, are fully described and illustrated by suitably chosen and well-reproduced photographs. Senior students should find them exceptionally useful. A positive Ehrlich test in the urine is said to contraindicate the administration of nearsphenamine, while this is true in most cases, the qualification might be added that the urine of pregnant woman and those who have imbibed alcohol during the previous 24 hours will also give this reaction, which in these patients is without dangerous significance.

The next edition of this admirable volume might include the recent observation that podophyllin, 25% in paraffin, successfully removes genital papillomata without causing the burning or irritation which is liable to accompany the recommended application of trichloroacetic acid.

No material changes have been made in the contents of this handbook, which will continue to succeed in its purpose of providing a concise epitome of the modern principles and practice of venereology, the pitfalls of diagnosis are detailed and the treatment recommended is practical and effective.

FILMS

There has recently been a considerable amount of discussion in the British medical press on the use of the film in medical education. Several different organizations, and a number of private individuals, have made medical films which have been regarded as having considerable educational value. For this reason it was decided that the time had come to start in this bulletin a section in which films of medical or biological interest could be reviewed. The first of these Film-sections appeared in No. 6 of Vol. 3. The article by Dr. Russell Reynolds, which opens the Film section in this number, is the first of a series in which medical men or biologists who have had practical experience in making films of medical interest will discuss their aims and some of their problems. Dr. Russell Reynolds is very well known as a pioneer of cineradiography, the subject of this article. In our next number we shall publish an article by an anaesthetist who played a considerable part in the production of a series of films on anaesthesia.

811

CINERADIOGRAPHY: ITS TECHNIQUE AND APPLICATIONS

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DMRE, FFR

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Charing Cross Hospital

The first "x-ray photographs" (as they were then called) of human subjects appeared in 1896, and the writer still possesses an x-ray plate taken by himself in that year, with his own home-made apparatus. It is interesting, therefore, to note that as early as 1897—only two years after Röntgen had made his discovery in November 1895, a Glasgow doctor, John Macintyre, attempted to produce an x-ray cinematograph film, and so became the first worker in the field of cineradiography. It must be remembered that cinematography was only in its

infancy, being developed, as we know it, in 1896. Of necessity Macintyre's choice of method was limited by the means at his disposal. He took serial radiographs of a frog's leg, moving its position slightly between each exposure. The completed series of plates was then re-photographed on to an ordinary cinematograph film for projection. The method he employed was clearly of an experimental value only, and was quite inapplicable to examination of the living human subject. Apart from the time required, the level of tolerance to x-rays was reached and passed, long before a sufficient number of radiographs could be taken. No further effort was made for many years to produce an x-ray cinematograph record.

But gradually apparatus became more powerful, and x-ray tubes more reliable, and the fluorescent screens used to convert the invisible rays into visible light were improved to give greater luminosity. Sensitivity of the photographic film emulsion was increased and lenses of wider aperture were designed. It then became theoretically possible to make cineradiograph films by two additional methods.

The first, or Direct Method, utilizes the power which x-rays share with light of affecting a sensitized photographic emulsion. Rays emitted by the tube pass through the subject under examination, and then strike the sensitized film which is momentarily clamped between two fluorescent or intensifying screens. The screens reinforce the direct action of the rays by the visible light which they emit when struck by the rays. This is, of course, a method now employed in normal radiography.

The second, or Indirect Method, employs a rather different principle. In this case, the rays passing through the patient, strike a fluorescent screen, and the shadows cast on this screen are photographed in the ordinary way with a cinematograph camera.

Many problems had to be solved before either method gave satisfactory results. In the examination of the living subject, the risk of over-exposure to x-rays, with consequent burning or injury, must constantly be borne in mind. X-rays cannot be focused, and this limits the scope of the Direct Method. If, for example, an attempt is made to take a cineradiograph film of a chest by this method, then each separate frame of the series must be at least as large in area as the projected dimensions of the chest under examination (approximately 38 x 30 cm).

It is not possible to obtain a true cinematographic effect at a projection speed of fewer than 12 frames per second and indeed

a higher speed than this is desirable. The operator would, therefore, be faced with the problem of running a film area of 180 square inches (about 1160 cm²) into position between two fluorescent screens 12 times every second, and holding it there, absolutely still, while the exposure is made. This allows, at the most, a time of only 1/24 of a second for the necessary movement. Assuming that a total exposure time of 10 seconds is needed for the completion of the movement of the part under examination, it follows that a strip of film 120 feet [36.6 m] long by 15 inches [38 cm] wide would be required. The difficulties of designing an apparatus capable of handling such a film are very great, and the cost of examination is prohibitive. Moreover, the problem of development still remains, followed later by reduction to standard size of 35 or 16 mm for projection.

Some workers have used the Direct Method and have had success with a restricted area of about 5 × 4 inches [12.5 × 10 cm] when speed in movement was not essential, e.g., filming the contractions of the gall-bladder. This method precludes examination of large areas, but allows records to be obtained of some of the organs, and rather circumscribed views of most of the joints. It is, however, a method for operation only in research institutions and laboratories and it cannot with advantage be used in private or hospital practice. Even with an exposure field reduced to 5 × 4 inches, film costs are high, and the problems of keeping the film free from vibration during exposure, and of processing, present many serious practical difficulties.

FIG 1 EXAMPLES OF 16 mm X-RAY PHOTOGRAPHY



Specimen prints taken from 16 mm films of normal hand-movements and of the chest in a case of pericarditis with effusion and adhesions

Difficulties of another kind face the operator who chooses the Indirect Method. The intensity of light emitted by the fluorescent screen is weak. It can be increased if the intensity of the beam of x-rays to which it is subjected is also increased, but this, of necessity means an added exposure-risk to the subject under examination. In addition, to make the greatest possible use of all the light available, a lens of very large aperture is required, together with a photographic film of great sensitivity. At the same time the film must be protected from the direct beam of x-rays which escapes beyond the fluorescent screen (about 3% only is absorbed by the screen). If sufficient light can be obtained, the method is simple in operation. The film is readily obtainable and, being of standard size, is easy to process and does not have to be reduced for ultimate projection.

The writer began his cineradiographic experiments in 1921, using the Indirect Method. From the outset, it was clear that the fluorescent screen would emit a satisfactory quantity of light only if the x-ray beam directed on to it were of high intensity. Under such conditions, the risk to the subject of over-exposure to radiation was considerable and the strain on the tube was great. A switch was therefore incorporated in the apparatus which synchronized the excitation of the tube with the opening of the camera-shutter. In this way, the exposure of the patient was reduced by half, and the strain on the tube was reduced to a corresponding extent.

In 1925, using the most brilliant screen available, together with the most sensitive photographic film and a wide-aperture lens (1.5) a film was obtained of a hand and wrist, at a speed of 1/8 of a second for each image. Reproductions of a child's thorax were obtained in 1/3 of a second and these results were shown at the International Congress of Radiology at Chicago in

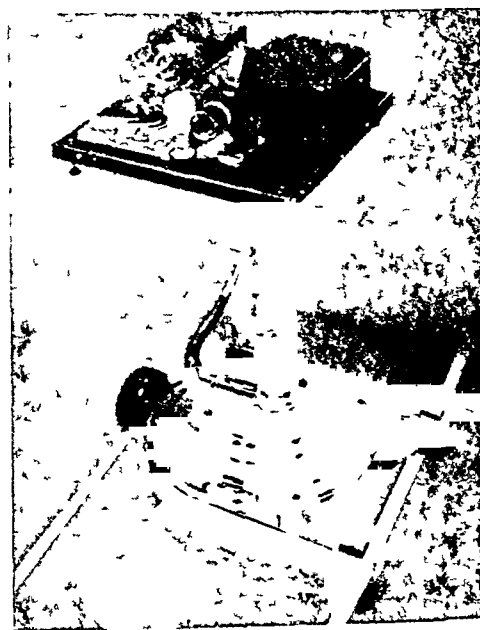
1927. These films of the thorax were, of course, useless for cinematograph projection, but they were the best which could be obtained at the time.

Experiments were resumed in 1933. By that date it was possible to obtain a more brilliant screen and new photographic films, a lens of wider aperture was also available (0.85). Results were most encouraging, and by 1934, adequate records had been produced of the movements of all joints except the hips and the lower spine, at speeds up to 12 frames per second (1/24 of a second exposure), and of the heart and stomach at slightly slower rate.

Since this time, there have been very marked improvements in the results. It has been found possible to reduce the intensity of the x-ray beam considerably, and still obtain records of joint movements at speeds up to 50 frames per second (1/100 of a second exposure). Films of the heart taken at 25 frames per second (1/50 of a second exposure) produced a slow-motion effect when projected at a slow speed. There has been a corresponding improvement in the rate at which films of the stomach may be taken (12 frames per second, 1/24 of a second exposure).

As exposures have been reduced, the risk to the subject under examination has been steadily diminished until, at the present time, the subject receives less than he would in an ordinary prolonged x-ray examination. Nevertheless, the method by which the recent films have been taken is essentially the same as that employed in the experiments of 1921, i.e. photography of the

FIG 2 CINERADIOGRAPHIC APPARATUS



Camera unit on adjustable pedestal

fluorescent-screen image with an ordinary cine-camera, and synchronization of the opening of the camera shutter with the excitation of the tube.

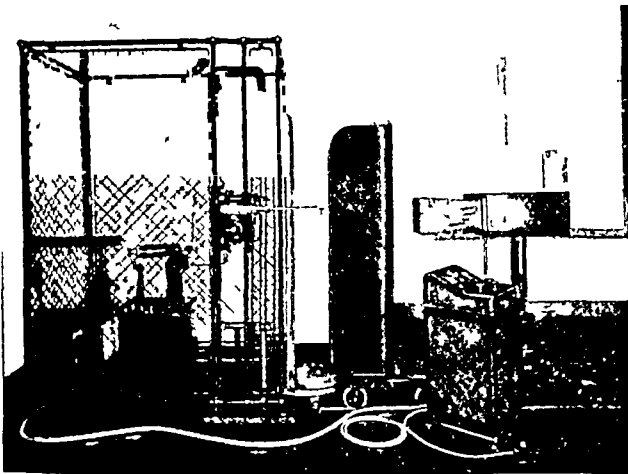
A total exposure-time up to 10 seconds (radiation-time up to 5 seconds) is ample for showing any cycle of movement. After development, the 16 mm film negative is printed and the parts are joined into a continuous band. Films of this size are so easily handled in comparatively short lengths, that all processing can be carried out quite simply. This band, containing complete cycles of the movements, can be threaded through the projector and allowed to run continuously while the action is studied.

During the course of his research, the writer has taken nearly 1,000 cineradiographic films—at least 70% of them of human subjects, and at no time has there been any evidence of over-irradiation. At a maximum, the patient does not receive more than about 64 r units for any single examination. At the present time, the method is quite simple, reliable and safe.

From the foregoing it will be clear that cineradiography not

only opens up a vast field in research, but will give invaluable aid in medical diagnosis. It is not yet possible to set a limit to its uses and applications, and although a great deal of experimental work has been carried out, much more is required before

FIG 3 CINERADIOGRAPHIC APPARATUS



Side view of complete unit

all its potentialities are assessed. Its value in the examination of the normal movements of joints is obvious, just as is the detection of possible causes of restricted movement, and later comparison of the degree of movement before and after treatment.

It is probable that, in the future, a cineradiographic record of the heart beat will be included in the complete medical examination of that organ as a routine procedure, but before this technique can be fully utilized in the diagnosis of abnormal conditions, further study of normal cineradiographic appearances is necessary.

Just as it is necessary to possess adequate knowledge of the normal appearance of an organ under examination in a "still" radiograph, before proceeding to the diagnosis of the abnormal, so it will be necessary to be equally familiar with the appearance in normal and abnormal movement in a cineradiograph film. The response of organs to the action of drugs offers another interesting field of study by cineradiography. It may be advisable to make films of the heart recording simultaneously the electrocardiograph tracing at the base of the film. This has already been successfully carried out by the writer, both with the cathode-ray oscilloscope and the Cambridge string electrocardiograph instruments. Needless to say, sound recording can always be incorporated.

Further examples of the uses to which cineradiography can be put in the medical sciences could be multiplied almost indefinitely. Nothing has so far been mentioned as to its application in medical education. Students assimilate knowledge far more easily if they can study the actual movements at leisure, and permanent records are always available.

In experimental physiology, cineradiography has already proved its worth and in experimental science generally its value has yet to be assessed.

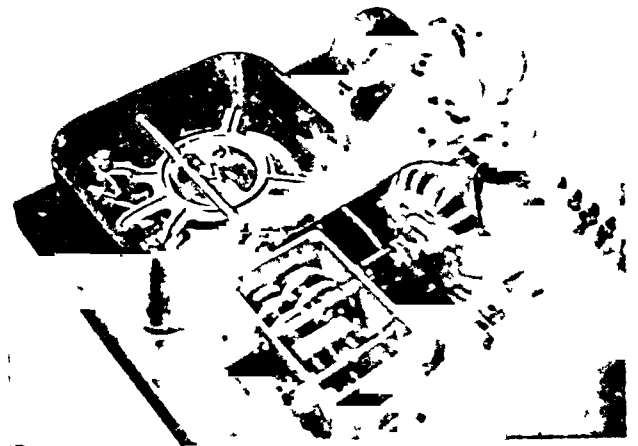
In February 1936 by the generosity of Lord Nuffield a cineradiographic apparatus as illustrated in this paper was installed at the Nuffield Institute of Medical Research, Oxford. The department was opened by the late Sir Farquhar Buzzard Bart, regius professor of medicine at Oxford and the author gave a demonstration of its use. Subsequently some experimental work with the apparatus was undertaken by Dr A. E. Barclay in 1939. He published a paper in conjunction with Sir Joseph Barcroft, F.R.S., Dr Barron and Dr K. J. Franklin on a radiographic demonstration of the circulation through the heart in the adult and in the foetus and the identification of the ductus arteriosus.

Apart from general examination of patients for diagnostic purposes and the recording of normal movements of healthy patients, several important pieces of research work have been carried out with the cineradiographic apparatus. In the Hunterian Lecture of the Royal College of Surgeons in January 1937, the author demonstrated the results of his research on the movements of the oesophagus, stomach and duodenum during the passage of an opaque meal. Valuable information was obtained of the exact mechanism during peristalsis and the passage of the meal.

In 1939 also this method of investigation was used to demonstrate the action of the Bragg-Paul pulsator. The films obtained were shown at a meeting of the Physiological Society of Great Britain (Cineradiographic films illustrating normal respiration and artificial respiration with the Bragg-Paul pulsator). The normal respiratory movements of a healthy male and female were shown, and the movements were observed when the depth of respiration was increased by the use of the Bragg Paul pulsator. The movements in the latter case are similar to those observed in deep breathing of the subject, increased diaphragmatic movement being evident as well as increase in the costal excursion. In the films of unassisted quiet breathing, the usual pause at the end of respiration can be seen and measured. This is not evident in the artificial respiration films when, however, a pause occurs between inspiration and expiration.

In conclusion it may be stated that only by the cineradiographic method of examination can one adequately study the functions of organs and joints and obtain complete records of movements. So far, movements have been observed only on screen examination, i.e. the fluorescent screen image, this necessarily has to be very rapidly carried out owing to the danger of over-exposure to x-rays. The radiologist has to be content with viewing the screen for a few seconds only and memorizes what he has seen. He can of course take an x-ray film at any given instant but this only records conditions at the particular moments of exposure. With a cineradiographic film, however, it is possible to obtain a permanent record of movement which can afterwards be studied at leisure. It is available at all future times for comparison with other cine films that may be made. It is necessary only to expose a short length of film showing one or more cycles of movement. The extremities of this film can be joined to make a band, which constitutes a complete record of the case. This record can be

FIG 4 CINERADIOGRAPHIC APPARATUS



Camera unit showing camera synchro and gear work and in erupor

Dr A. E. Barclay, F.R.S., 1939, J. Physiol., 91, 1-10. The author has been assisted by Dr A. E. Barclay, F.R.S., and Dr K. J. Franklin, F.R.S., in the work on the circulation through the heart in the adult and in the foetus and the identification of the ductus arteriosus.

kept with the patient's notes and can be examined with the patient at any future consultations that may be necessary, wherever the patient may be

The cost of production is small, not exceeding that incurred in having a complete x-ray examination in the usual way

I should like to acknowledge here the valuable help I have received in the latter part of this work from my sons Dr Seymour Reynolds and Major S R Reynolds, R A M C

The four films reviewed here were recently shown in London by Dr P de Fonbrune to an audience of biologists and medical men. Dr A G Sanders, of the Sir William Dunn School of Pathology at Oxford, has provided the following notes on these unique films. Dr Sanders has himself had experience in the making of films in the field of experimental pathology

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FOUR REMARKABLE FRENCH MICROBIOLOGICAL FILMS

These four films were produced by Drs Comandon and de Fonbrune in the laboratory of cinemicrography of the Pasteur Institute in Paris. This laboratory is situated in the annexe at Garches, so as to be well away from the vibrations caused by the traffic of the city. Here has been developed the technique of microdissection to a very high degree, and such fine manipulations as the rupture of individual erythrocytes, or the transplantation of the nucleus from one amoeba to another, are performed with apparent ease. To perform these delicate operations special instruments were devised and also the apparatus needed to make and manipulate these instruments. These are demonstrated in the first film

I NOUVEAUX APPAREILS POUR LES MICRO-MANIPULATIONS

The extremely fine micropipettes, needles, scalpels, hooks and other tools used for these operations are made under direct microscopical observation with an apparatus called the "micro-forge"

Most of the instruments are made of pyrex glass, though soft glass is sometimes used for special purposes

A fine glass tube or rod is first sealed into the end of a wider one, which is clamped into the instrument-holder of the micro-forge. The fine end is brought into the field of view of a horizontal microscope with an inclined eyepiece

Heat is supplied by a V-shaped platinum-iridium filament, which can be electrically heated to any desired degree. Cooling, if needed, is supplied by jets of cold air from an electric blower. Both the instrument under construction and the filament can be moved in all necessary directions by suitable control knobs. The film shows in detail how several different types of instruments are made

For microdissection with these extremely fine instruments a special type of micro-manipulator has been devised. It consists of two parts connected only by rubber tubes. The receptor consists of a heavy metal base on which is a frame carrying three metal tambours, similar to those found in aneroid barometers. The diaphragms of these tambours are set at right-angles to one another. A complex lever is connected to the centres of the three diaphragms and bears at its free end a clamp for holding the micro-needle or other instrument. An alteration in the air-pressure within any tambour moves its diaphragm in or out, and consequently displaces in the corresponding direction the lever and the instrument held by it

The tambours of the receptor are connected by three rubber tubes to the manipulator. On the base of the manipulator are hinged two glass-and-metal syringes with very well-fitting pistons. They are at right-angles to one another and are con-

nected to the tubes from the tambours controlling the two horizontal movements of the lever in the receptor. The pistons of these syringes are connected to a ring encircling a vertical lever, which can be rocked about a universal joint at its lower end. Movements of the knob on top of this lever are therefore communicated pneumatically to the micro-needle, whose point faithfully copies them on a much smaller scale

Vertical movements are accomplished by rotating the knob on top of this controlling lever. This moves the piston of a third syringe, incorporated in the body of the lever and connected by the third rubber tube to the tambour responsible for vertical movements of the lever bearing the needle

2 EXPERIENCES SUR LES ERYTHROCYTES DE GRENOUILLE PARASITE PAR UNE HEMOGRE-GARINE (LANKESTERELLA)

The oval, nucleated erythrocytes of a frog are shown in this film. Some are parasitized by a species of *Lankesterella*. The movements of the parasite within the red cell can be seen, and also the astonishing ease with which the parasite leaves one cell and enters another. The cell-wall appears to present no barrier at all to the parasite, nor does haemoglobin escape from the cell at the point of entry or exit of the parasite

The red cells are also shown when being pierced with a glass micro-needle. Although the needle appears to be more pointed than the front end of the parasite, there is obviously some difficulty in piercing the cell-wall with the needle. After puncture there is usually very little escape of haemoglobin from the cell, as the cellular protein rapidly forms an impermeable patch over the hole

Occasionally, however, the patch gives way and the cellular contents, including the nucleus, escape

3 ABLATIONS ET GREFFES DE MOYEAUX CHEZ UNE AMIBE

For studying the slow movements of an amoeba, time-lapse cinemicrography has been particularly useful and has revealed things which would not have been apparent by direct observations. The gross movements as well as the intracellular protoplasmic movements of a healthy amoeba are quite characteristic when photographed in this way

The technique of removal of the nucleus by microdissection is then demonstrated. After this operation the cell shrinks and stops moving about, though movement of protoplasm within the cell still continues. Fresh food is not ingested, but any food-particles already engulfed are slowly digested. The cell without its nucleus may, however, be still alive after 48 hours

Into such a cell it is possible to graft another nucleus from a healthy cell. A few minutes after such an operation the powers of locomotion and ingestion of food are restored, and the protoplasmic movements return to normal. Such grafted cells have been observed to undergo normal mitotic division soon after operation

4 ETUDE D'UN CHAMPIGNON PREDATEUR DE NEMATODES

A curious fungus, *Dactylaria brocopaga*, is found in garden soil. When grown in pure culture in the absence of a certain microscopic nematode worm on which it is parasitic, the mycelium is very similar to many other fungi. When, however, the nematode is present, the fungus produces little rings, some 25 μ in diameter, attached to the hyphae. Each ring consists of three cells

If one of the nematodes tries to pass through the ring these three cells suddenly expand inwards and so grasp the worm firmly

Projections from the inner aspects of the cells enter the body of the worm and through them the fungus first kills and later digests the worm. The whole process takes from 12-24 hours

Other similar fungi catch and hold their prey by producing networks of mycelium which are sticky or from which sticky buttons protrude

Microscopic nematodes and other creatures becoming entangled in the sticky network are killed and digested by the fungus

The stickiness of some of these fungi can be demonstrated by touching them with a glass needle held in a micromanipulator

*

These four films are of the greatest interest to specialists in the subjects with which they deal, but are scarcely less interesting

[Overseas medical teachers and medical societies who wish to borrow or purchase prints of the films indexed or reviewed here should apply to the nearest British Council representative (see back cover) or direct to the Editor, quoting the numbers used below, e.g. Film 10 Inclusion of a film in this section does not imply that a print will be available for loan or purchase. In some cases it will be, and in others it will not.]

813/14 Movement of the Tongue in Speech

made by Realist Film Unit, 1945, slow motion with photography by Kodak Research Laboratory, owned by ICI, 16 mm sound, 444 ft. [130 m.], 35 mm. sound, 1112 ft. [330 m.], 2 reels, Technicolor and black and white, 13 minutes

This review by Sir Richard Paget the distinguished authority on human speech, is reproduced from *Documentary News Letter* (1945, 5, 93) by permission of the editors

Movements of the human tongue and lips during speech as seen in a male patient with part of his right cheek removed by a surgical operation. Technicolor shots at normal speed are associated with black and white shots of the same action, speeded up 40 times

A somewhat gruesome film but of great technical interest. The first instance (it is believed) in which the actual movements of the tongue have been made visible. Only the more forward movement can be seen, as the portion of the patient's cheek which has been removed only extends a little over one inch from the corner of his mouth. But many points of interest to students of phonetics and articulation are disclosed. Thus the backward curvature of the tongue in forming the English "T,"

to all biologists. They could also be shown with profit to students of biology in schools and universities

Technically they are all of the highest quality. Those who have experience in cinemicrography can best realize what an enormous amount of time and really hard work must have been needed for their production
A G Sanders

and the withdrawal of the tongue as a whole to form the backward closures (K, G and ng) [English] can be actually seen, though the final closure and release are hidden

The longitudinal growing of the tongue in articulating "sh" is made visible, as also the 'pantomimic' upward and downward movement of the tongue in articulating the word "high". Slow motion pictures of some of the words articulated are also shown. In each case the voice of the commentator is heard giving the words which the patient then repeats after him

For instructional purposes it would be of advantage if the film could be supplemented by a short preliminary statement, together with a cartoon film showing a complete vertical section of a mouth and throat (as seen from the right) so that the relation between the movements actually shown in the film and the various accompanying movements (not visible) might be made clear

The importance of good articulation needs to be stressed in all teaching of English speech. This film is a notable achievement, and should be the forerunner of a series of cartoon films derived from x-ray and other observations, showing the movements of articulation and the gestural relationship between the short words in English (and indeed in all languages) and the fundamental meanings which they convey

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SCIENTIFIC INSTRUMENTS

A MEDICAL TOUR OF THE 30th EXHIBITION OF SCIENTIFIC INSTRUMENTS & APPARATUS

Many new types of apparatus as well as several instruments already mentioned in a previous number (Vol. 3, No. 6) of this bulletin were shown publicly for the first time at the Thirtieth Exhibition of Scientific Instruments and Apparatus, organized by the Physical Society in London early in January, 1946. Electrocardiograms using cathode ray tubes were shown by A. C. Cossor and the Clifton Instrument Company, the Marconi four-channel electroencephalogram was working, Multitone had a fine heavy-duty audiometer, and the Evans-Mendelsohn pyrometer was demonstrated

There were x-ray generators designed for crystallography and industrial research, but not for medical use. However, there was a fine selection of measuring equipment of medical interest. Messrs. Baldwin displayed a production model of the Farmer electrometer (*Proc. phys. Soc.*, 1942, 54, 435), now designed to operate from electric mains or self-contained batteries, in conjunction with his (Farmer's) midjet ionization chambers (*Brit. J. Radiol.*, 1945, 18, 148). This instrument will be of great value both for routine clinical control and for research in radiotherapy departments. On this stand, too, was a production model of the radium-detector commonly known as the 'clucking hen'. Marconi showed a prototype of the Farmer dosimeter designed for deep x-ray therapy (*Brit. J. Radiol.*, 1944, 17, 160), it looks superficially like a small version of the Mekapion, but works on a different principle, this instrument will be marketed soon. Clifton Instrument Company showed the 'Sphygmoscope,'

an instrument¹ designed to give visible indication by cathode-ray tube of the systolic and diastolic blood-pressure of a patient during anaesthesia. Multitone showed a compact model of Caplan's electroconvulsant apparatus, and a fine group hearing-aid installation designed for schools for deaf children: this equipment is one of which these pioneers have every reason to be proud, for perfect reproduction at any desired intensity is obtained by a special differential cut-out adjusted to each pupil's requirements. In addition, they showed a small deaf-aid of the amplifier type which will be so low in price that they have styled it 'The People's Aid'

In the other half of the exhibition, devoted to demonstrations of research techniques and equipment, the National Physical Laboratory (NPL) showed the apparatus they have evolved for testing the leak of the piston of a hypodermic syringe and its barrel, this apparatus has been used in the determination of a British Standard for hypodermic syringes. On another floor the NPL showed the apparatus which they have designed for standardizing Haldane haemoglobinometers, they are now working on a standard for the Sahli method

The medical exhibits were only a very small portion of the whole. The largest crowd centred round the Metrovick electron microscope, and the hall demonstrating radar equipment was unapproachable for the crush. Yet, strangely enough, wartime equipment was not much in evidence, and some splendid new equipment designed specifically for peacetime needs was on show. Chas. Baker and Cooke Troughton & Simms both showed research microscopes of new design, while Pullin (Optics) displayed a splendid heavy duty projector with air-blast cooling designed for projecting film-strip and substandard colour slides, this should find a wide demand in equipping new lecture theatres

This annual exhibition popular enough in pre-war years was phenomenally successful after 6 years' absence. The entire issue of 4,000 catalogues was sold out 1½ hours after the exhibition opened, and on the third (and last) day a queue over 2,000 yards long was waiting for admission. Three days is not enough for an exhibition of this importance, and we hope it will be possible to keep it on longer next year
B. Stanford

¹ [This instrument will be fully described in our next number.—Ed.]

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5 September 1945

- The nature of fibrositis 1 The myalgic lesion and its secondary effects a reflex theory (M Kelly) 1-7
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 Rheumatism in Sweden (W S C Copeman) 17-19

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- The adsorption fluorescence estimation of mepacrine and stilbamidine (A J Henry & D N Grundley) 1-7
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Centenary of Anaesthesia

THERE are several dates of importance in the early history of anaesthesia, and the centenary of some of these has already been celebrated. The year 1946, however, marks the conclusion of a hundred years of uninterrupted progress, and to accept this year as the centenary of anaesthesia is not to ignore the claims of earlier pioneers who, for one reason or another, did not, as Morton did in 1846, effectively initiate the universal adoption of anaesthesia for surgical operations.

It is remarkable that inhalation anaesthesia, which was developed almost exclusively in America and Britain, has for so long remained virtually an Anglo-American specialty. In other countries, local and, more recently, intravenous methods have been favoured. However, modern surgical requirements, especially in the fields of plastic and thoracic surgery, have made some forms of inhalation anaesthesia almost obligatory, and there would seem to be little doubt that inhalation methods will be considerably extended in countries which have hitherto been content to rely mainly upon other techniques.

The extension of inhalation anaesthesia carries with it the implication that the surgeon can no longer be responsible for the administration of the anaesthetic. If the patient is to receive the full benefit of available techniques of anaesthesia, it is essential that the choice and administration of the anaesthetic should be the responsibility of the specialist anaesthetist. This involves the question of the proper status and responsibilities of the anaesthetist. In recent years this question has been a subject of discussion in Britain and America, and in the latter country the word "anesthesiology" has been devised to denote a range of duties which includes much more than the technical details of the administration. This neologism may have its detractors, but it is useful because it emphasizes the contrast between the newer conception of the "anesthesiologist" and the older conception of the anaesthetist as a pure technician. Dr John S. Lundy, of the Mayo Clinic, has recently (*Curr Res Anesth* 1946, 25, 41) defined anesthesiology as "the administration of anesthetics and associated activities. These activities include the use of blood and blood substitutes and the support of the patient in shock, during anesthesia and afterward, the use of stimulants in connection with support of the patient's circulation and the stimulation of his breathing and reflex activities of his body."

There are some peculiarities of the anaesthetist's vocation. In other branches of medical practice, the outcome of therapeutic procedures is often conjectural, and their choice may be founded more upon pious hope or uncritical faith than on reasoned expectation. The task of the anaesthetist, however, is precise and unequivocal, and the techniques that he employs are clearly designed to effect a known result which is an end in itself. Every induction of general anaesthesia is an act of applied pharmacology, and the anaesthetist is performing upon the human subject the equivalent of a physiological demonstration. Nevertheless, although anaesthesia has come so far since the days of Morton, the bold empiric, progress was for many years confined to the perfection of practice and technical methods, and the anaesthetist did not fully exploit his unusual advantages. More recent developments give ground for the belief that there will be an increasing field for collective scientific work by chemists, physiologists, pharmacologists, and anaesthetists, and even the physicist has a part to play in the solution of special problems.

In this number of *British Medical Bulletin* no attempt has been made to produce an account of the practice of anaesthesia. The contributors deal with experimental and clinical subjects, the common feature of which is relative novelty. As is appropriate on the occasion of such an important centenary, a considerable amount of space has been allotted to historical material. Readers who wish to obtain practical information on modern anaesthesia will find their needs admirably served by Dr C. Langton Hewer's *Recent advances in anaesthesia* (5th edition, London, 1944) and *Modern anaesthetic practice* (2nd edition, 1946) edited by the late Sir Humphry Rolleston and Prof. A. Moncrieff, and other well-known textbooks.

* * *

DR J. H. BURN, who contributes two papers, is professor of pharmacology in the University of Oxford. He has for many years been concerned with problems of biological standardization, and has published an indispensable book on that subject (*Biological standardization*, Oxford, 1937). He devised methods for estimating the antidiuretic hormone of pituitary (posterior lobe) extract, the potency of oestrogenic substances and the therapeutic activity of organic arsenic compounds. Professor Burn has also been interested in physiological problems, he has studied the vasodilator fibres present in the sympathetic system of different species, and also the part played by sympathetic impulses and by adrenaline in the contraction of skeletal muscle. This has led to a study of the interaction of acetylcholine and adrenaline in the nervous system.

DR D. WHITTERIDGE is university demonstrator in physiology and Fellow of Magdalen College, Oxford. He has worked on the physiological effects of blast during the war and has continued to investigate the mechanisms of various forms of dyspnoea which occur in blast, gas poisoning, anaesthesia and heart failure.

DR EDITH BULBRING is university demonstrator in pharmacology at Oxford. She has worked on biological assay and devised methods for the estimation of cortical hormone, of growth hormone, of local anaesthetics and of atropine substitutes. She is especially interested in studying the influence of adrenaline on nervous transmission and has published work on the effect of adrenaline on nerve action-potentials on synaptic trans-

mission in the sympathetic ganglion and on neuromuscular transmission

DR E C DODDS has been Courtauld professor of biochemistry in the University of London since 1925 and is director of the Courtauld Institute of Biochemistry at the Middlesex Hospital. He has worked for many years on the chemical and physiological properties of internal secretions, with particular reference to sex hormones and their chemical interrelationship with other substances and the search for a synthetic analogue for the oestrogenic hormone which led to the synthesis of stilboestrol, hexoestrol and dienoestrol. In 1939 he was Cantor lecturer, Royal Society of Arts, in 1934, Goulstonian lecturer, Royal College of Physicians, and in 1935, Harvey lecturer, New York University. Professor Dodds is the author (with Dr G E Beaumont) of *Recent advances in medicine* (11th edition, London, 1943) and of numerous articles in scientific journals. He is also editor of the *Journal of Endocrinology*.

DR H R ING is Reader in pharmacological chemistry in the University of Oxford, and formerly held a similar position at University College, London. During 1939-1944 he was an experimental officer of the Ministry of Supply, engaged mainly on research problems concerning the defensive aspects of chemical warfare. He is a chemist, who has specialized in the study of the relations between the chemical structure and properties of drugs and their pharmacological properties.

DR DAVID S EVANS and DR K MENDELSSOHN have previously contributed to the *Bulletin* and a note on their work has appeared in No. 6 of Volume 3.

PROFESSOR L P GARROD has made two previous contributions to the *Bulletin*, and notes on his work appear in No. 3 of Volume 1 and No. 1 of Volume 2.

DR C LANGTON HEWER is senior anaesthetist to St Bartholomew's Hospital and vice-president of the Association of Anaesthetists of Great Britain and Ireland. He has held the office of president of the section of anaesthetics of the Royal Society of Medicine and that of examiner in anaesthesia to the Royal Colleges of Physicians and Surgeons. In the first world war he served in the RAMC (Special Reserve of Officers). Dr Hewer is a member of the combined Anaesthetics Committee of the Medical Research Council and the Royal Society of Medicine, and on their behalf investigated the anaesthetic properties of trichlorethylene. He is the author of *Recent*

advances in anaesthesia and analgesia, to which reference has already been made above.

DR H J V MORTON is the author of several publications on various aspects of anaesthesia and is a member of the council of the section of anaesthetics of the Royal Society of Medicine. He has been for some years senior anaesthetist at Hillingdon County Hospital. A large proportion of the thoracic surgery in the county of Middlesex is performed at this hospital, and Dr Morton has had considerable experience in anaesthesia for this type of work.

DR A J W BEARD has been a demonstrator of physiology at St Bartholomew's Hospital, and, in addition to the appointments that he holds as anaesthetist, he is physician to the Wimbledon and Nelson Hospitals. In his article, Dr Beard depicts the anaesthetist's responsibility as covering the general condition of the patient before, during, and after the administration of the anaesthetic.

DR BARBARA M DUNCUM was for some years on the staff of the Wellcome Historical Medical Museum, London, and was there in charge of the records department, which collected, correlated and indexed information relating to the history of medicine. Since joining the Nuffield department of anaesthetics, University of Oxford, in the autumn of 1938, Mrs Duncum has made a study of inhalation anaesthesia during the first half-century of its development. The results of her researches are shortly to be published by the Wellcome Historical Medical Museum, through the Oxford University Press.

DR G S W ORGANE is honorary anaesthetist to the Westminster Hospital, the Infants' Hospital, Vincent Square, London, and the Royal Eye Hospital, and consulting anaesthetist to the Nelson Hospital. He has made several contributions to the literature of anaesthesia, and for the historical section of this number he has provided a brief general survey of contemporary anaesthetic techniques. In the film section, he describes the making of a series of films on anaesthesia.

MR A CHARLES KING is a well-known manufacturer of anaesthetic equipment who has for some years made a study of the historical evolution of apparatus for inhalation anaesthesia. In the course of his studies, Mr King has acquired an interesting and comprehensive collection of books on anaesthesia in the English language.

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THE TESTING OF LOCAL ANAESTHETICS

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When a new compound has required testing for activity as a local anaesthetic, the methods hitherto available have been rough methods allowing an approximate measure of potency to be obtained provided that a good deal of care was taken. For example, it has been customary to carry out a test on the cornea of the rabbit, dropping a solution of known concentration into the conjunctival sac to see if anaesthesia followed. The usual aim has been to find the lowest concentration which produced anaesthesia. The practical difficulty of finding this threshold concentration is greater than might be supposed, and a recent proposal made by Chance & Lobstein (1944) has proved to be an important step forward. They applied a given solution to the cornea of the guinea-pig at a certain time, and at regular intervals they tested the

corneal reflex by touching the cornea with a light object, not once, but six times, and determined what proportion of the six stimuli were effective. It might be expected that the cornea would either be anaesthetized fully or not anaesthetized at all. This is not so. Anaesthesia may, of course, be complete, and then all stimuli fail. There is, however, a stage in which the anaesthesia begins to diminish, and from that point until it has completely disappeared the proportion of stimuli which evoke a response slowly increases. By testing a compound on the eyes of a group of guinea-pigs and determining for each concentration the mean rate of disappearance of anaesthesia, it is possible to make an accurate comparison between one compound and a known substance like cocaine which is chosen as a standard. Thus Chance & Lobstein have made a new and valuable approach to the problem of testing local anaesthetics.

Intracutaneous-wheel Anaesthesia in Guinea-pigs

The principle of the method of Chance & Lobstein has now been applied by Bulbring & Wajda (1945) in this department to the intracutaneous-wheel test in guinea-pigs proposed by McIntyre & Sievers (1937, 1938). In this test the substance to be tested is injected in a volume of 0.2 ml into the skin of the back, in the middle of an area which has been clipped and shaved the previous day. The same volume of a standard

such as procaine is also injected a few cm away. Having outlined the area of the injection with ink, the observer then tests the area six times at intervals of 5 minutes, giving six light pricks with a pin to which the response in an anaesthetized area is brisk and regular. At each test the number of stimuli to which there is no response is recorded, and when these numbers are added up, the sum gives an indication of the degree of anaesthesia achieved by the solution injected.

TABLE I RESULTS OF WHEEL TEST IN GUINEA PIGS (nupercaine)

Time (minutes)	0.0125%			0.025%		
	Guinea pig 1 (Back)	Guinea pig 2	Guinea pig 3	Guinea pig 1 (Front)	Guinea pig 2	Guinea pig 3
5	5	6	6	6	6	6
10	3	4	2	3	6	5
15	3	2	2	3	2	5
20	1	0	1	3	1	4
25	0	—	0	1	0	0
30	—	—	—	0	—	—
	Guinea pig 4 (Front)	Guinea pig 5	Guinea pig 6	Guinea pig 4 (Back)	Guinea pig 5	Guinea pig 6
5	5	3	4	6	6	6
10	2	3	4	3	5	6
15	0	0	3	2	3	4
20	—	—	0	0	3	4
25	—	—	—	—	3	3
30	—	—	—	—	0	0
	mean sum for 30 minutes 9.8 ± 1.08			mean sum for 30 minutes 17.5 ± 1.75		
Time (minutes)	0.05%			0.1%		
	Guinea pig 7 (Front)	Guinea pig 8	Guinea pig 9	Guinea pig 7 (Back)	Guinea pig 8	Guinea pig 9
5	6	6	6	6	6	6
10	4	6	6	6	6	6
15	4	5	5	6	6	6
20	4	4	3	6	6	6
25	1	4	2	6	6	6
30	1	1	1	5	6	6
	Guinea pig 10 (Back)	Guinea pig 11	Guinea pig 12	Guinea pig 10 (Front)	Guinea pig 11	Guinea pig 12
5	6	6	5	6	6	6
10	6	5	4	6	6	6
15	6	5	4	6	6	6
20	6	5	4	6	6	6
25	6	4	3	6	5	6
30	2	3	3	6	3	6
	mean sum for 30 minutes 25.3 ± 1.86			mean sum for 30 minutes 35.2 ± 0.66		

Number of pricks (out of six) failing to elicit a response after intracutaneous injection of nupercaine in guinea pigs (compare Fig. 1)

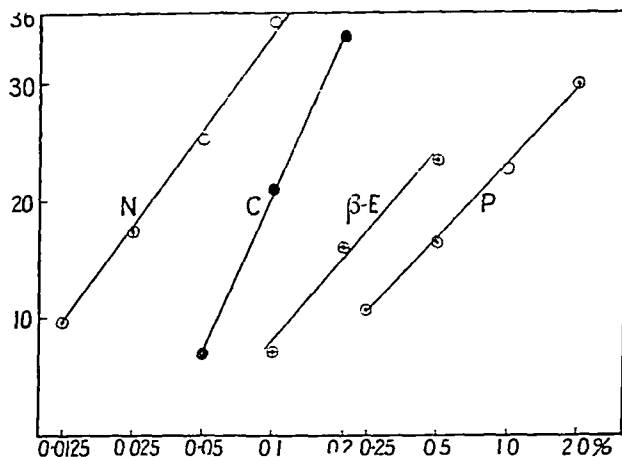
An illustration of the results which are obtained is given in Table I, in which nupercaine was used. Two experiments are set out, the first in the upper half of Table I is the comparison of the effect of 0.0125% nupercaine with that of 0.025% nupercaine. The weaker solution was injected into the hind part of the back of guinea-pigs 1, 2 and 3, and also into the front part of the back of guinea-pigs 4, 5 and 6, the stronger solution was injected into the front part of the

back of Nos. 1, 2 and 3, and into the back part of the back of Nos. 4, 5 and 6.

When tested at 5 minutes after injection, the area at the back of No. 1 did not respond to a prick 5 times out of the 6 applications. At 20 minutes the area failed to respond only once. The sum of the figures for the back area of guinea-pig No. 1 is seen in Table I to be 12. The mean sum for all areas injected with the solution 0.0125% is 9.8. When the solution was 0.025%, the mean sum is 17.5, for 0.05%, the mean sum is 25.3, and finally for 0.1%, the mean sum is 35.2. These figures for the mean sum (which represents the degree of anaesthesia) are plotted in Fig. 1 as ordinates, the abscissae being the logarithm of the concentrations. The degree of anaesthesia so expressed was found to bear a linear relation to log concentration.

In addition to nupercaine, cocaine, β -eucaine and procaine were tested in this way, and the results of these tests also appear in Fig. 1. For each of these substances the relation of the degree of anaesthesia to log concentration was found to be linear, and the straight lines for nupercaine, β -eucaine and procaine were approximately parallel. The line for cocaine was steeper. The fact that linear relations were found for each substance indicates that the method is a good one and gives a means of obtaining a quantitative comparison of two substances for local anaesthetic activity on sensory nerve-endings in the skin of the guinea-pig. In comparing two substances it is obviously important that the comparison should be made simultaneously, injecting both substances into each guinea-pig. It would be unwise to test the two compounds at different times, or to test them on different guinea-pigs.

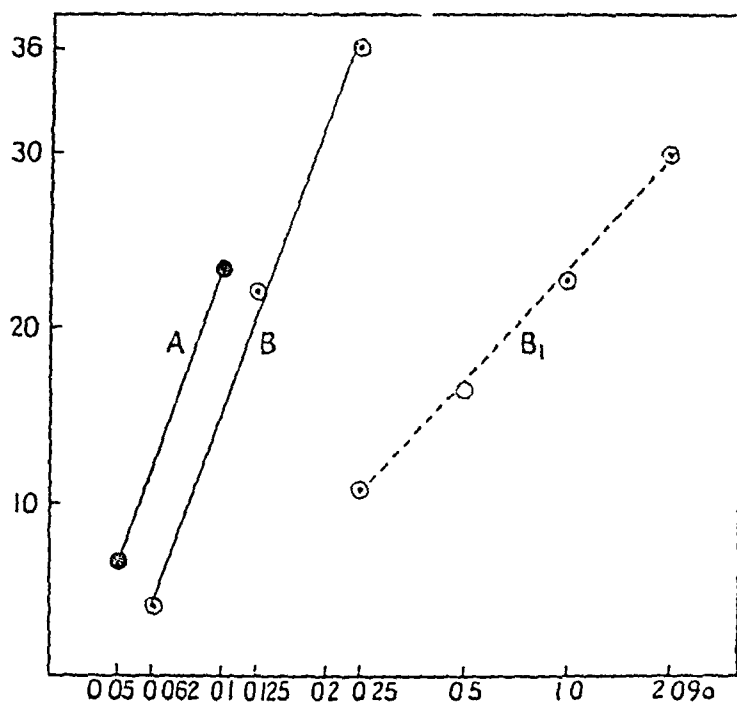
FIG. 1 RESULTS OF WHEEL-TEST IN GUINEA PIGS



Abscissae = dosage in terms of the logarithms of the concentrations of the anaesthetic agents used
Ordinates = degree of anaesthesia, as measured by the number of stimuli (out of 36) which elicited no response
N = nupercaine C = cocaine, β -E = β -eucaine, P = procaine (compare Table I)

The fact that cocaine gave a line in Fig. 1 differing in slope from the lines given by the other substances was thought likely to be due to the vasoconstrictor action which cocaine possesses. There was at least no other known property of cocaine to which the difference might be attributed. A direct comparison was therefore made between a solution of cocaine and a solution of procaine to which adrenaline was added.

FIG. 2. WHEEL-TEST EFFECT OF ADDITION OF ADRENALINE TO PROCAINE SOLUTION



Abscissae = dosage in terms of the logarithms of the concentrations of the anaesthetic agents used

Ordinates = degree of anaesthesia as measured by the number of stimuli (out of 36) which elicited no response

A = cocaine, B = procaine + 0.001% adrenaline, B₁ = procaine alone (from Fig. 1)

The results indicate that the difference in the inclination of the line for cocaine from those of other anaesthetic agents tested is due to its vasoconstrictor action

in a concentration of 1 in 100,000. The result of this comparison is shown in Fig. 2, in which A represents the results with cocaine and B the results with procaine mixed with adrenaline. The dotted line B₁ is the same as the line for procaine alone given in Fig. 1. The line for procaine plus adrenaline is obviously parallel to the line for cocaine, and in the presence of adrenaline lower concentrations of procaine become effective.

Plexus-anaesthesia in Frogs

Sollmann (1918) described a method of estimating local anaesthetic action in frogs in which the solution was applied to the sciatic plexus. The frog is decapitated and the upper part of the spinal cord is destroyed down to the 3rd vertebra. A transverse incision is made in the abdominal wall just below the sternum. The viscera are removed through this opening, carefully exposing the lumbar plexus without damaging it. The frog is pinned by its forearms so as to hang vertically. The solution of the local anaesthetic, dissolved in 0.7% saline, is poured into the abdominal cavity, the amount used is unimportant so long as the plexus is submerged. In Sollmann's method the aim was to find the least concentration which would abolish the motor response of withdrawing the legs when the feet were dipped in acid.

Bülbring & Wajda have modified this test in the following way. The time was noted when the solution was put in the abdominal cavity. Once every minute a beaker containing dilute HCl was brought up so that the feet were immersed, the immersion was not more than 10 seconds and the feet were then washed with water to remove the acid. The first

solution used was 0.05N HCl, when the frog failed to react, a stronger solution, 0.1N, was used, and finally 0.2N was used. The time when each solution failed to evoke a response was noted. When there was no response to 0.2N, stronger acid also failed.

The important observation was the length of the time elapsing between the application of the local anaesthetic and the moment when the response to 0.2N HCl failed. This interval was determined in the manner described, beginning with weaker acids in order to avoid damaging the sensory nerve-endings by the application of stronger acid than necessary. Four frogs were tested at the same time. The results of examining three concentrations of cocaine by this method are given in Table II. When the concentration of

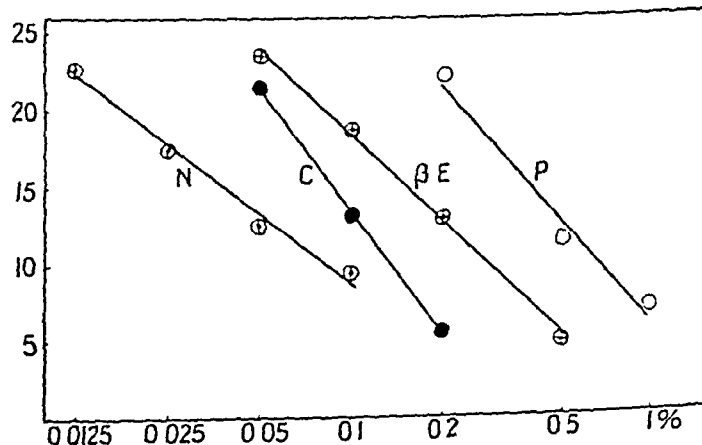
TABLE II RESULTS OF PLEXUS-ANAESTHESIA IN FROGS

Concentration of cocaine %	Frogs	Time for anaesthesia to dilute HCl (minutes)			Mean time for anaesthesia to 0.2N HCl (minutes)
		0.05N	0.1N	0.2N	
0.05	1	3	9	17	20.25 ± 4.3
	2	7	18	23	
	3	4	28	28	
	4	2	9	13	
0.1	5	4	6	8	9.7 ± 1.0
	6	4	8	11	
	7	3	4	12	
	8	5	7	8	
0.2	9	2	3	5	4.5 ± 1.3
	10	1	7	8	
	11	0	0	2	
	12	1	2	3	

Time taken for the development of plexus-anaesthesia in frogs (compare Fig. 3)

0.05% was used, the mean time for anaesthesia to 0.2N HCl was 20.25 minutes, when the concentration was 0.1%, the mean time was 9.7 minutes, finally, when the concentration was 0.2%, the mean time was 4.5 minutes. A comparison of the results in different frogs treated with the same concentration shows that there is much variation among the frogs (compare, for instance, frog 10 and frog 11).

FIG. 3 RESULTS OF PLEXUS-ANAESTHESIA IN FROGS



Abscissae = dosage in terms of the logarithms of the concentrations of the anaesthetic agents used

Ordinates = interval (minutes) elapsing before negative response
N = nupercaine, C = cocaine, β-E = β-eucaine, P = procaine (compare Table II)

When the figures for the mean time are plotted as ordinates against the logarithms of the concentrations used, a linear relation was again observed, the results for cocaine are marked C in Fig 3. Once again the lines for nupercaine, β -eucaine and procaine were more nearly parallel to one another than they were to the line for cocaine, it is difficult to account for the difference in slope in this test by the vasoconstrictor action of cocaine, a vasoconstrictor effect could scarcely come into play. To what the difference is due is not known.

The Relative Potency by the Two Methods

The relative potency of the three synthetic anaesthetics expressed in relation to that of cocaine is given in Table III. These results were obtained in direct comparison of each substance with cocaine hydrochloride. Since the slope of line relating log concentration to effect of cocaine differs from that of the other substances it would probably be better

to use procaine hydrochloride as a standard of comparison

TABLE III POTENCY RELATIVE TO COCAINE OF THREE LOCAL ANAESTHETICS

Substance	Intracutaneous wheal (guinea pigs)	Plexus-anaesthesia (frogs)
Cocaine hydrochloride	100	100
Procaine hydrochloride	13.5	41.5
β eucaine	51.3	51.3
Nupercaine	282.5	169.5

Summary

Two new methods of making a quantitative comparison of local anaesthetics are described, both illustrating various principles which are important in making quantitative comparisons of any kind in living tissue, whether the tissue is an isolated organ taken from an animal, or the whole animal, or a human subject.

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CHANGES IN ACTIVITY OF PULMONARY RECEPTORS IN ANAESTHESIA AND THEIR INFLUENCE ON RESPIRATORY BEHAVIOUR

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 E BULBRING, M D, M A

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A frequent observation made by anaesthetists is that respiratory disturbances occur during the induction of anaesthesia with trichlorethylene. The patient's respiration may become so shallow and rapid that severe asphyxia results before the stage of deep anaesthesia can be reached.

Reflex Control of Respiration

It is generally agreed that the rate and depth of respiration are largely determined by nervous impulses from the lung. These nervous factors have long been familiar under the name of the Hering-Breuer reflex. This reflex has essentially two parts: expansion of the chest inhibits further activity of the inspiratory muscles, and under certain circumstances collapse of the chest initiates inspiratory efforts. In most present-day text-books an attempt is made to explain the whole Hering-Breuer reflex on the basis of a single set of afferent fibres from the lungs. These fibres are stimulated by the expansion of the alveoli, and their impulses travel up the vagus nerves to the respiratory centre. They are usually known as stretch-fibres, and have been studied in detail by Adrian.

The alternative view that there are at least two sets of afferent fibres concerned in the Hering-Breuer reflex was maintained by Head, and by Hammouda & Wilson. Recently,

strong physiological evidence has been obtained for the existence of a second set of fibres arising in the lungs and causing inspiration. So far as histological evidence is concerned, some nerve-endings have been described in the walls of the pulmonary arterioles with fibres running to the vagus. These fibres, which do not come from the alveoli but from the small vessels in the lungs, are probably responsible for the deflation-reflex. They are stimulated both when the lungs collapse, as can best be demonstrated in animal experiments by suction of air from the lungs (see below), and also during an inspiratory effort against obstruction (Whitteridge, unpublished work). Thus, not only the stretch-reflexes, but the co-ordinated activity of both sets of fibres seem to influence the normal pattern of respiration, balancing, as it were, inspiration and expiration. It is known that the respiration becomes slow and deep after cutting the vagi, presumably because both the stretch-reflexes and the deflation-reflexes are abolished.

Effect on Stretch-receptors of Artificial Respiration in the Spinal Cat

Trichlorethylene produces rapid and shallow breathing which is very readily reversible. An investigation was therefore carried out comparing the effects of trichlorethylene on the vagal afferent impulses with those of other anaesthetics which do not usually produce severe respiratory disturbances.

For the study of the activity of vagal endings in the lungs we have used cats. Electrical changes in the vagus nerve were observed in a single vagal fibre, which was obtained by dissecting the vagus with sharp needles. Impulses were recorded with an amplifier and a cathode-ray tube. In most single-fibre preparations the afferent impulses come from the stretch-receptors and have a respiratory rhythm. Their frequency increases with expansion of the lungs, and the highest frequency is reached at the end of inspiration.

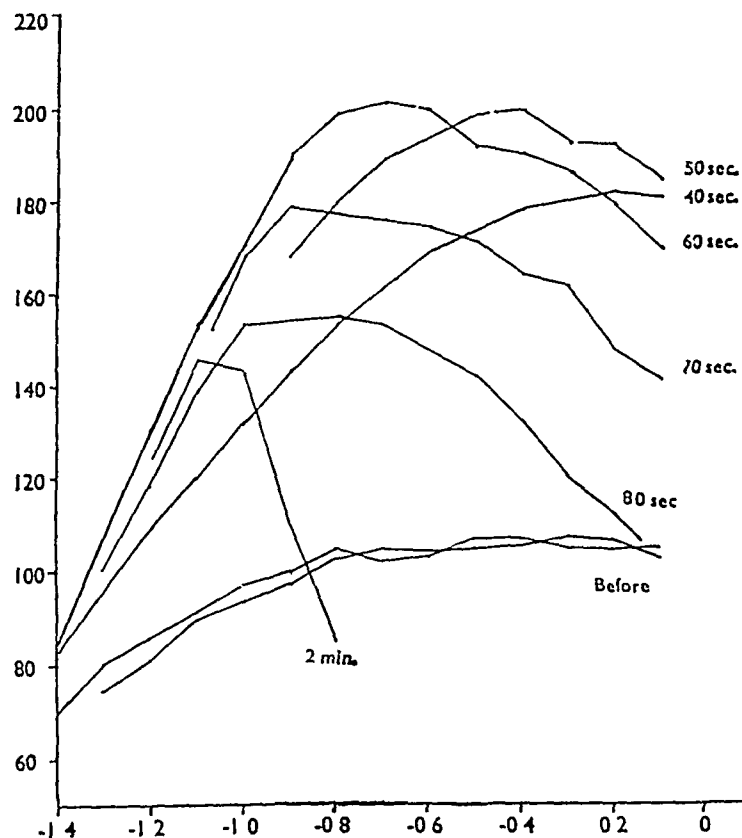
In spinal or decapitated cats, artificially respired with a pump, the majority of these fibres from stretch-receptors in the lungs were inactive during expiration, they became active

only during inspiration, and the frequency of discharge increased with inflation of the lungs. With an inflation of 100 cm³ the highest frequency of discharge in different fibres varied from 50-250 impulses per second. Within limits this peak frequency was directly proportional to the pump-stroke, and with a slow rate of ventilation (15 per minute) the peak frequency of discharge at constant inflation remained the same within $\pm 5\%$ for several hours.

Sensitization of Stretch-receptors by Trichlorethylene and other Volatile Anaesthetics

When trichlorethylene was added to the inspired air, there was a steady increase in peak frequency of stretch-impulses in spite of the fact that the output of air from the pump was constant. With 0.5%-2% trichlorethylene this increase in frequency reached 50%-140% above the initial value, where it was maintained. With higher concentrations, the peak frequency was reached at an earlier point of the inspiratory phase, but then declined more rapidly until the impulses ceased half-way through the pump stroke, this was followed by complete failure of the receptor (see Fig 1). During recovery which occurred very rapidly after withdrawal of the trichlorethylene, there was a further period of increased activity before the frequency returned to its initial value.

FIG 1 EFFECT OF TRICHLORETHYLENE ON THE PULMONARY STRETCH-RECEPTORS IN THE SPINAL CAT



Spinal cat, lungs inflated by a pump with constant volume. Ordinates = frequency of stretch-impulses per second, as observed with the cathode-ray oscillograph on a single vagal fibre. Abscissae = time in $\frac{1}{10}$ sec before the end of inflation at 0. The initial sensitization and gradual failure of a stretch-receptor during single pump-strokes is shown at different times after exposure to 3-4% trichlorethylene.

Other volatile anaesthetics tested, i.e. chloroform, ether, di-vinyl ether, ethyl chloride, cyclopropane and nitrous oxide, had the same type of effect as trichlorethylene on stretch-receptors. Chloroform acted very rapidly. With low concentrations (1%), a very rapid increase in frequency could be observed for a short time, after which the frequency slowly declined, but with higher concentrations this increased activity almost immediately gave way to complete failure. Recovery was rapid. With ethyl ether the changes in frequency occurred less rapidly. Di-vinyl ether and ethyl chloride were found to be very potent. Cyclopropane and nitrous oxide produced a rise in frequency of 50-100%, which quickly reached a steady level. No sign of failure was seen even during brief inflation with 100% of either of these two anaesthetics.

There was the possibility that the effects observed were due to the action of the anaesthetics on the heart. In order to exclude this, experiments were carried out in which the lungs were perfused with blood by a pump. When recording from a single vagal ending in such a preparation, the same effects of trichlorethylene on stretch-receptors were obtained as those described in the whole animal, the effects could not therefore be due to an action on the heart, nor could any method of causing asphyxia produce comparable changes in the sensitivity to expansion of the lungs.

Considering the results so far, it seemed that in general the initial effect of all volatile anaesthetics tested was an increase in the sensitiveness of stretch-receptors in the lungs. The difference between the anaesthetics lay in the rate at which this sensitization decayed during continued exposure to the same concentration of anaesthetic. Cyclopropane and nitrous oxide caused a hyperexcitability of stretch-receptors throughout exposure. Taken in order of potency, ethyl chloride, chloroform, di-vinyl ether, ethyl-ether and trichlorethylene all caused a stimulation of stretch-receptors followed by paralysis. Thus there was no fundamental difference between them.

Effect of Sensitization of Stretch-receptors on Spontaneous Respiration in Decerebrate Cats

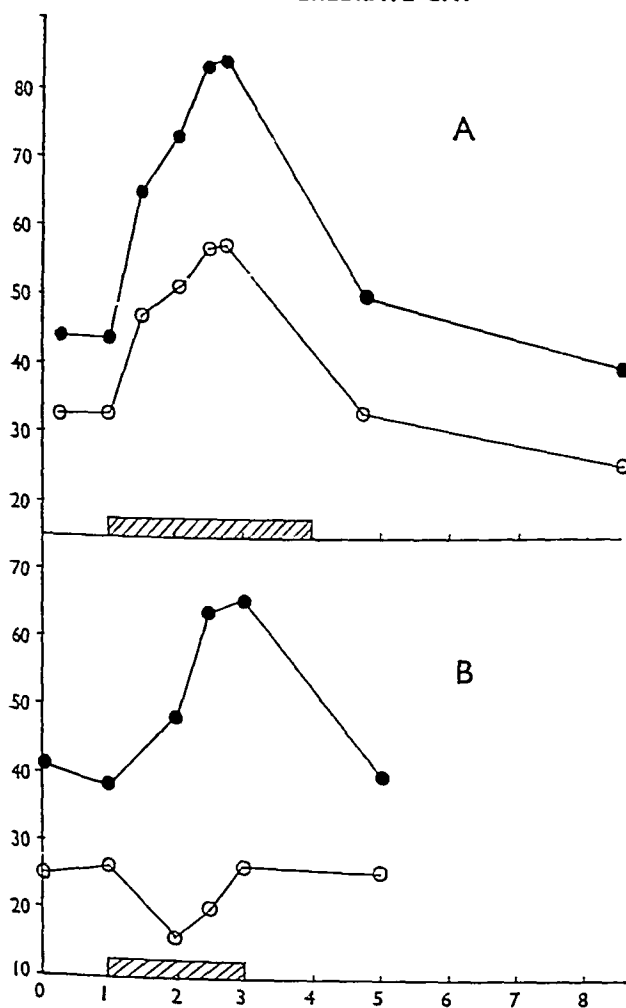
In spinal animals there was practically no means of measuring the depth of anaesthesia. As they were artificially respired with a pump the point of respiratory arrest by the anaesthetic could not be observed. In a few experiments, in which the pressure in the right ventricle was recorded, there was some evidence of a toxic effect on the heart. In order to see whether failure of the stretch-receptors preceded respiratory arrest and whether the sensitization of the stretch-receptors modified respiration as a whole, observations were made on decerebrate cats breathing spontaneously. The animals were enclosed in a respiration-chamber with the tracheal tube connected externally. In this way records of respiratory rate and depth, and the residual air in the chest at the end of expiration, were obtained simultaneously with a record of vagal activity.

In such cats, with one or both vagi intact, the effect of a chemical stimulus to the respiratory centre, 5.5% CO₂, was to cause an increase in depth of respiration which was closely parallel to an increase in peak frequency of discharge from the stretch-receptors. However, the effect of trichlorethylene, ether or chloroform was to cause a decrease in lung-volume at the end of inspiration simultaneously with an increased frequency of vagal discharge (see Fig 2). This initial shallow

breathing was then clearly due to the sensitization of the stretch receptors. Under ether, failure of discharge occurred well before respiratory arrest. Under trichlorethylene and chloroform, respiratory arrest occurred at about the same time as failure of discharge from the stretch receptors.

The respiratory rate and the volume of air in the lungs at the end of expiration seemed to vary independently of the sensitivity of stretch receptors. Trichlorethylene increased both the respiratory rate and the volume of air retained in the chest very markedly, ether often caused an increase

FIG 2. EFFECTS OF CO₂ AND ETHER ON PULMONARY STRETCH RECEPTORS AND DEPTH OF RESPIRATION IN THE DECEREBRATE CAT



Decerebrate cat breathing spontaneously
Ordinates = frequency of stretch impulses per second and lung-volume in cm³
Abscissae = time in minutes

The time-course of changes in frequency of discharge from a stretch-receptor (dots) and the volume of air in the chest (circles) at the end of inspiration are shown
A = during administration of 5.5% CO₂ B = during administration of 4.5% ether

Note that in A the frequency of stretch impulses increases with increased distension of the lungs whereas in B the frequency of stretch impulses increases while the distension of the lungs is less

followed by a decrease in both, while chloroform had very little effect on either. Cyclopropane had little effect on the volume of air in the chest at the end of expiration, but caused some slowing of the respiration. As it was impossible to ascribe these different effects to an action on stretch-receptors, on which all these anaesthetics have qualitatively similar effects, the behaviour of other afferent endings in the lungs was investigated.

Effects of Anaesthetics on the Deflation-Reflex

It seemed that stimulation of extrapulmonary receptors was unlikely to be of great importance since vagotomy almost abolished the effects of trichlorethylene on respiration. But, as has been mentioned above, there are in the lungs separate receptors which are stimulated by deflation and cause inspiration. Head has devised a method for detecting inspiratory efforts by recording the activity and the tone of a slip of diaphragm. For anatomical reasons this can be done only in rabbits. With intact vagi, as Head has shown, inflation of the lungs leads to abolition of the resting tone of the diaphragm and slowing of the respiration. On the other hand, suction of air from the chest leads to an increase of diaphragm-tone and increased respiratory rate if the suction pressure does not exceed 2 cm Hg. In our experiments a standard period of 15 seconds' suction of 1.3-1.6 cm Hg was applied, and the response was always an acceleration of respiratory rate. Cooling of the vagi to 4° C blocks the impulses from stretch-receptors which arrest inspiration, whereas impulses causing inspiration still reach the centre. Only after cooling the vagi to 1° C are the reflex effects of deflation on diaphragm tone and respiratory rate abolished.

Thus, some of the immediate effects of anaesthetics on respiration can be separated by cooling the vagi. At a temperature of 4° C, deflation-reflexes are still obtainable, whereas stretch afferents are completely blocked. The sequence of events in an animal with the vagi cooled to 4° C was as follows. The immediate effect of exposure to ether or trichlorethylene was an increase in diaphragmatic tone and in the amplitude of the contractions of the slip of diaphragm, with comparatively little change in rate. This increased tone subsided within a few minutes during continued administration of ether, but with trichlorethylene a gradually increasing tone was observed.

During the first few minutes after induction, suction of air from the chest produced a more pronounced increase in diaphragm-tone and greater acceleration of respiration than before the anaesthetic. On continuing the ether however, there was less and less acceleration which finally disappeared, while the acceleration-effect of deflation persisted throughout exposure to trichlorethylene. Thus, the reflexes causing acceleration of respiratory rate were first stimulated and then paralyzed by prolonged exposure even to low concentrations of ether, while trichlorethylene caused a slight prolonged stimulation.

Conclusion

Anaesthetists have reported respiratory disturbances especially rapid and shallow breathing, during anaesthesia with trichlorethylene. In our experiments we have tried to find an explanation for these disturbances by investigating the change in activity of pulmonary receptors during anaesthesia with a number of different volatile anaesthetics. The effect of trichlorethylene was compared with that of ether, chloroform, di-vinyl ether, ethyl chloride, cyclopropane and

nitrous oxide From the experiments on cats there can be little doubt that all the volatile anaesthetics tested increase the excitability of the pulmonary stretch-receptors, and that this increased excitability is largely responsible for the reduction in the depth of respiration Thus, shallow breathing may be produced by all these anaesthetics alike, the difference between them being only one of degree

On the other hand, the rate of respiration is affected differently by the anaesthetics tested Evidence has been obtained in rabbits that those deflation-reflexes which produce acceleration of breathing, are briefly stimulated but then paralyzed by ether, whereas they are stimulated

throughout exposure to trichlorethylene The increased rate of respiration during administration of trichlorethylene is therefore probably due to the cutting short of expiration as well as of inspiration

As the normal pattern of respiration is determined by the co-ordinated activity of both the stretch-reflexes and the deflation-reflexes, the sensitization of both is believed to account for the clinically familiar disturbances of respiration during anaesthesia, and in particular for the rapid and shallow breathing which is so conspicuous with trichlorethylene

The work described here has been the subject of a fuller report elsewhere (*J Pharmacol*, 1944, 81, 340-359)

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THE SEARCH FOR MORPHINE SUBSTITUTES

E C DODDS, M V O, D Sc M D, F R C P, F R S

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Until the 19th century, the remedies used in medical practice were either inorganic mineral salts or crude extracts from plants As the study of organic chemistry progressed, these crude extracts were analyzed, their active constituents were isolated and their constitution determined From this the next step was to try to synthesize these substances in the laboratory from such materials as coal tar, etc, and a further step was taken when attempts were made to improve on nature by altering the formula of a substance slightly and so enhancing its therapeutic effects

Some Early Synthetic Remedies

A very good example of the progressive steps leading to the discovery of a new remedy is the work which led to the introduction of aspirin The willow-bark, or *Salix alba*, was known to the ancients as an antipyretic In 1827, Leroux extracted from willow-bark the bitter glycoside called salicin From salicin Piria in 1838 made salicylic acid In 1844, Cahours made the same salicylic acid from oil of wintergreen This marks the end of the first stage, the isolation of the active principle from the natural source

The next stage was accomplished by Kolbe and Lautemann, who in 1860 prepared salicylic acid from phenol However, salicylic acid itself has only a limited therapeutic use owing to its irritant qualities, so the next stage was to try to modify the molecule in such a way as to enhance the good effects and diminish the bad This was accomplished when Dreser introduced aspirin, or acetylsalicylic acid, in 1899

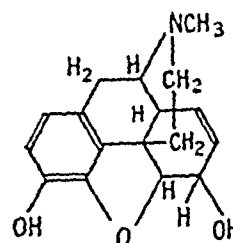
The earliest record of the production of an entirely synthetic remedy was the synthesis of chloral by Liebig in 1832 He produced this by the chlorination of absolute alcohol, which is the method used to-day Chloral hydrate, produced by the cautious addition of water to chloral, was introduced into medicine as a hypnotic by Liebreich in 1869 Liebreich thought that chloral hydrate would be broken down to chloroform in the body, but in this of course he was wrong

Other achievements along the same lines were the synthesis from coal tar of acetanilid by Cahn & Hepp in 1886, and later of phenacetin, and the introduction of barbitone by Fischer & von Mering in 1903

The Opium Alkaloids

Opium, which has been used in medicine for centuries, is now known to consist of a mixture of alkaloids which are the active principles, and of other substances which have no therapeutic value Up till the end of the 18th century only crude extracts of opium were available, but in 1816 Serturmer described the isolation of the most potent of the opium alkaloids, morphine (Fig 1) Subsequently 5 other

FIG 1 MORPHINE



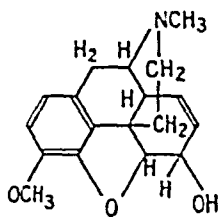
alkaloids were isolated, namely codeine, thebaine, papaverine, and narceine Narcotine had previously been isolated by Derosne The three alkaloids responsible for the analgesic properties of opium—morphine, codeine and thebaine—are built up on the phenanthrene-ring system As these compounds are related in chemical structure, so are they in biological activity, the differences between them being in the degree, rather than in the nature, of their activity Thus the analgesic, respiratory-depressant, convulsant, emetic and other effects of morphine are all reproduced in codeine, but in codeine the analgesic and depressant effects are weaker and the convulsant effects stronger

One very undesirable property shared by all the phenanthrene alkaloids of opium is the liability to cause addiction. Drug addiction became such a serious problem in the United States that a special committee was set up to try to find synthetic analogues for morphine which would reproduce the analgesic properties without the undesirable side-effects Since there appeared to be a definite relationship between chemical structure and biological activity, it was thought that the best way to tackle the problem would be to try to find out if possible what parts of the morphine molecule are specific for its different effects

New Compounds Prepared by Substitution

The first approach made was to try the effect of substitutions in the groups attached to the phenanthrene nucleus, and in particular the phenolic and alcoholic OH groups. Comparing morphine with the other alkaloids in this series, it is seen that the masking or replacement of these groups makes a considerable difference to the pharmacological action. Codeine (Fig 2), for instance, in which the phenolic,

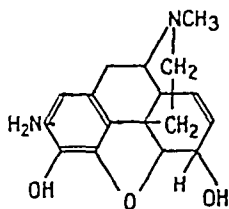
FIG 2. CODEINE



OH is replaced by OCH₃, is much more convulsant and much less analgesic and narcotic than morphine. A large number of compounds was made and, on the whole, it was found that substitutions in the alcoholic OH group enhanced the analgesic effects. Unfortunately, however, as the analgesic effects were enhanced, the toxicity and convulsant effects were increased too, so that these compounds were of no practical value.

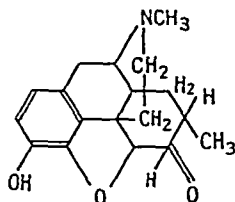
A further method that was tried was that of nuclear substitution, for instance the introduction of a basic amino group at carbon -2 (2-aminomorphine) (Fig 3). This caused

FIG 3. 2-AMINOMORPHINE



a decrease in the morphine-like properties. However, one substance produced along these lines, methyl dihydromorphinone (Fig 4), has been found to be of therapeutic value, as it is twice as effective in analgesic action and its duration of action is as long as that of morphine. In the cases in which it was tried, no emetic or respiratory depressant action was observed.

FIG 4. METHYL DIHYDROMORPHINONE



Building on the Phenanthrene or Similar Nuclei

Yet another method was to start, not from the morphine molecule itself, but from the simple phenanthrene nucleus, or

from some other nucleus, such as dibenzofuran or carbazol. The general formulae of these are shown in Fig 5. The most

FIG 5



effective analgesic among the derivatives from the phenanthrene nucleus was 3-py-tetrahydroiso-quinolino-4-hydroxy-1,2,3,4-tetrahydrophenanthrene. The carbazol derivatives appeared to be the most promising of all the synthetic substances, with high analgesic and narcotic effects, low toxicity and little emetic action. The most active member of this series was 9-methyl-2(1-hydroxy-3-diethyl amino) propyl carbazol. Of the substances submitted to clinical trial the most promising was methyl dihydromorphinone.

Synthetic Analogues

Another group of workers (Dodds, Lawson & Williams, 1944) approached the problem from a rather different angle. Bearing in mind that stilboestrol, which bears only loose chemical relationship to the naturally-occurring oestrogens, is able to replace these in every way, these workers considered the possibility that synthetic analogues might be found for other naturally-occurring substances containing the phenanthrene ring system.

As a starting point diphenylethylamine was tested, and then 17 derivatives of this were prepared and investigated. Their code-numbers, chemical names and formulae are given in Fig 6.

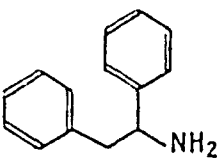
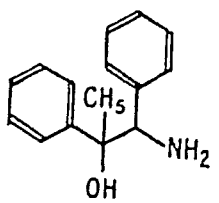
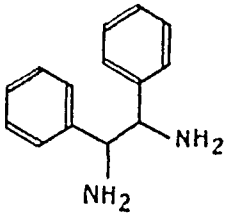
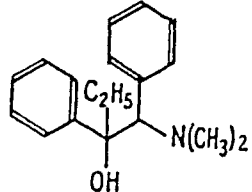
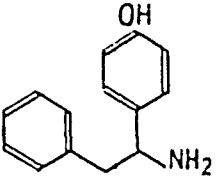
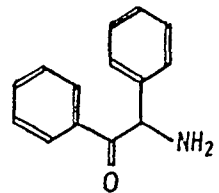
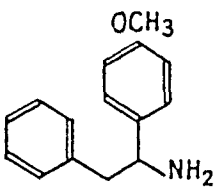

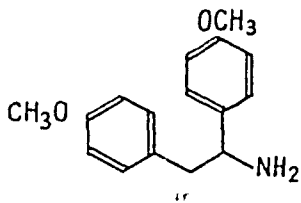
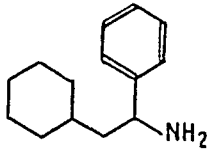
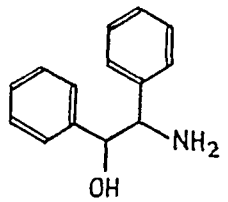
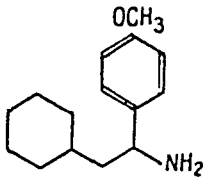
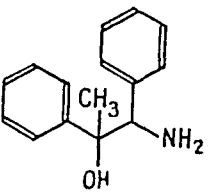
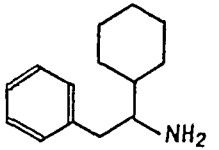
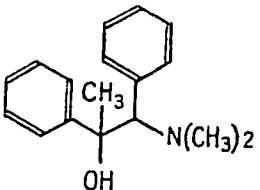
Animal Tests The criteria of the biological tests were depression of the righting-reflex in rats, rise in the blood-sugar in rabbits, and the effects of intramuscular injections in cats. Five of the compounds were tested clinically.

The synthetic compounds were all found to have less capacity than morphine for depressing the righting-reflex in rats. There did not appear to be any coherent relationship between chemical structure and pharmacological activity. It was found that the di-amino compound (M2) appeared to have no depressant activity at all. The β -hydroxy compound (M4) and the compounds with hydroxy or methoxy groups attached to one, or both phenyl rings (M15, M14, and M1) were less active than the parent compound (M3). On the other hand, the cyclo-hexyl compounds (M16 to M18) were more active, but more toxic, than the parent compound.

With regard to the effects on the blood-sugar of rabbits, diphenylethylamine was found to have a marked capacity for raising the blood-sugar, although the doses required were larger than the doses of morphine required. Addition of an amino group in the β -position was found to increase the activity (M2), as also the addition of a single hydroxy group to the α -phenyl ring (M15), but methylation of this phenolic hydroxy group (M14) markedly increased the activity. The cyclo-hexyl compounds (M16 to M18) appeared to be the most active of all.

The effects of the compounds on cats were difficult to assess, as the number of animals available was very small and cats vary very much in their individual response to the

FIG 6 DIPHENYLETHYLAMINE AND RELATED COMPOUNDS

Code No	Chemical Name	Formula	Code No	Chemical Name	Formula
M3	$\alpha\beta$ diphenylethylamine		M6	β hydroxy- $\alpha\beta$ diphenyl-n butylamine	
M2	$\alpha\beta$ diphenyl-ethylene-diamine		M9	β hydroxy- $\alpha\beta$ diphenyl n-butyl dimethylamine	
M15	α (p hydroxyphenyl)- β -phenyl ethylamine		M12	α -amino deoxy benzoin	
M14	α -(p anisyl)- β -phenyl ethylamine		M7	dimethylamino benzyl-phenyl-ketone	
M1	4,4'-dimethoxy- $\alpha\beta$ -diphenylethylamine		M16	α phenyl- β -cyclohexyl ethylamine	
M4	β -hydroxy- $\alpha\beta$ -diphenyl ethylamine		M17	α -(p-anisyl)- β -cyclo-hexyl ethylamine	
M5	β -hydroxy- $\alpha\beta$ diphenyl-n-propylamine		M18	α -cyclo-hexyl- β -phenyl-ethylamine	
M8	β -hydroxy- $\alpha\beta$ -diphenyl-n-propyl dimethylamine				

effects of morphine. Diphenylethylamine and its β -hydroxy derivative (M4) both produced pupil dilatation and hyperexcitability in cats. Addition of methyl or ethyl groups also in the β -position (as in M5 or M6) appeared to increase the activity, and it was still further increased by methylation of the amino nitrogen (as in M8 and M9). Three of the compounds (M7, M16 and M18) produced vomiting, and others produced nausea, licking of the lips, and salivation.

Clinical Tests Five of the compounds, M3, M4, M2, M7, and M18, were tested clinically. For this purpose they were administered orally to patients suffering from pain due to malignant disease and who were having morphine at 4-hourly intervals. The substances to be tested were substituted for

the morphine without informing the patient. Substances M2, M7 and M18 were found to be inactive. M3, when given in doses of 200 mg every 3 hours, was found to relieve the pain, but mental confusion developed after about one hour. When given to normal persons, M3 produced elation and slight muscular incoordination. M4 was tried on 14 patients and gave complete relief of pain in all cases without any signs of mental confusion or undesirable after-effects.

Extensive clinical investigation, however, showed that this series of compounds relieved only pain associated with nerve-pressure. They were found to be completely effective in cases of carcinomatous growth pressing on nerves, but appeared to be without any activity on pain caused by

inflammatory processes and similar conditions. It must, of course, also be emphasized that substances of this series at present investigated are of only theoretical interest, and are not suitable for adoption into clinical practice. It may well be, however, that further investigations in this series would succeed in producing substances of actual clinical importance.

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SYNTHETIC SUBSTITUTES FOR ATROPINE

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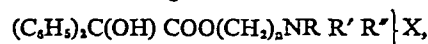
During the war need arose to investigate synthetic mydriatics which might be used in place of atropine if supplies of the latter became inadequate. Synthetic atropine was thought to present a far too difficult manufacturing problem and the only synthetic mydriatic of the atropine type in common use, viz. eucatropine, is a much less powerful drug. The supply of homatropine is, of course, dependent upon the same sources as atropine.

Atropine is an ester of an amino-alcohol (tropine) and a phenylhydroxypropionic acid (tropic acid). Jowett & Pyman (1910) had shown that synthetic esters of tropine display marked mydriatic activity on local application to the eye only when the esterifying acid contains both a phenyl and a hydroxyl group. Braun, Braunsdorf & R  th (1922), Fromherz (1933) and other workers had also shown that the tropine part of the molecule could be replaced by simpler and more readily accessible amino-alcohols without complete loss of mydriatic activity. The problem resolved itself into finding the optimal combination of amino-alcohol and acid.

The work of Blicke and his collaborators (Blicke & Maxwell, 1942; Blicke & Kaplan, 1943) suggested that benzoic acid was the most suitable acid; it contains two phenyl groups and a hydroxyl, and consequently fulfils the conditions laid down by Jowett & Pyman. Unfortunately Blicke made no quantitative comparison of his compounds with atropine, and it is therefore difficult to judge the relative merits of the different amino-alcohols which he used; moreover, several of his mydriatic benzoic esters were also described as excellent local anaesthetics, a result which throws doubt on the truly atropine-like character of their mydriatic action.

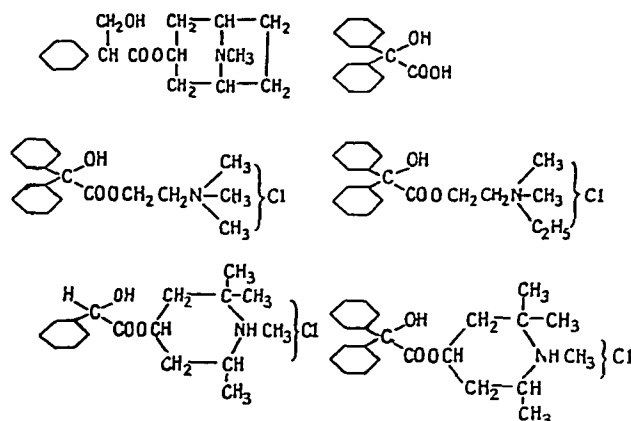
The mydriatic effect of atropine is the result of an antagonism to acetylcholine and it was thought that the same effect might be achieved by a suitable choline ester, for this reason the benzoic and tropic esters of choline were first prepared. Benzylcholine chloride had about 30% of the mydriatic effect of atropine (in mice) and tropylcholine

chloride about 15%. These results led to a systematic study of benzoic esters of the general formula



where R, R' and R'' are alkyl groups, X is a halide anion, and n = 2 or 3. Before discussing the results of this study, it may be well to outline briefly the method used to estimate mydriatic activity.

FIG. 1. FORMULAE OF ATROPINE AND SYNTHETIC SUBSTITUTES INVESTIGATED



Methods

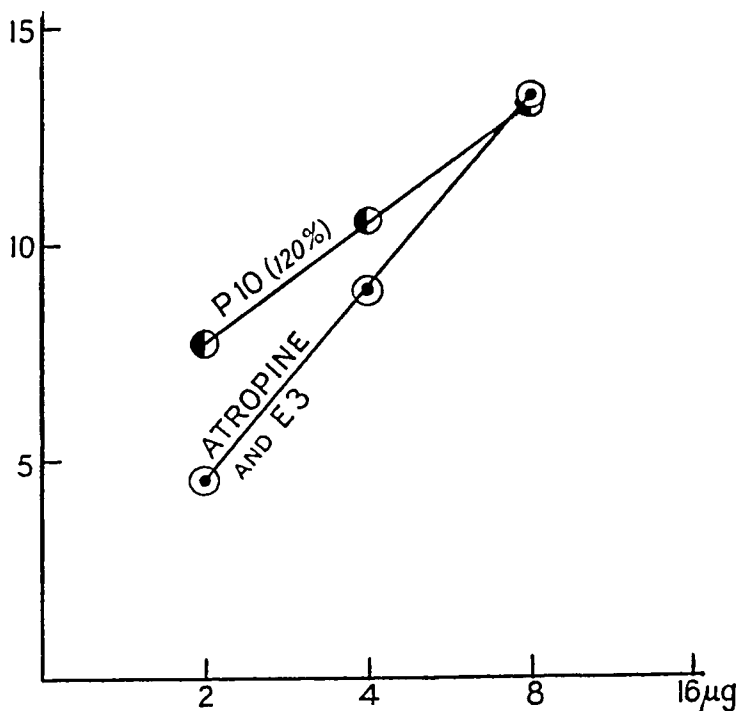
All the early work on synthetic mydriatics involved a comparison of the effects produced by the instillation of standard solutions of atropine and of the synthetic substances into the eyes of cats or rabbits; this method allows only a qualitative judgment of relative activity. A quantitative method was described by Pulewka (1932) in which the drug is injected into mice and the diameter of the pupil is measured directly by means of a binocular microscope with a scale in the eyepiece.

Groups of mice, of approximately uniform weight (15-20 g), are injected intraperitoneally with 0.2 ml of the solution to be tested and the size of the pupil is measured in the arbitrary units of the eyepiece scale. The effect of atropine reaches its maximum in 15 minutes and begins to decline after 25 minutes; for this reason, readings of pupil-diameters are made between 15 and 20 minutes after the injection.

The effect of a given dose of atropine varies in different groups of mice and even within the same group at different times, for this reason, the effect of two or three different doses of atropine in different groups of mice should always be determined simultaneously with that of a range of doses of the substance under test. In practice it is convenient to use 5 mice in a group and to inject 3 groups with different doses of the substance under test and 3 groups with different doses of atropine.

When atropine is given in the dosage range 0.002-0.008 mg per mouse the mean diameter of the pupil in a group 15 minutes after the injection is directly proportional to the logarithm of the dose (Fig. 2). By plotting the results obtained with atropine as in Fig. 2, the mean effect of a dose of the substance under test can be equated to that of a dose of atropine, and consequently the potency of the substance can be expressed as a percentage of the dose of atropine which would produce the same mean effect. The curves relating log dose to mean effect of the synthetic mydriatics are also linear, but they are often not parallel to that of atropine, in such cases it is impossible to derive a potency figure which will hold true at all doses, but an average figure over a four- or five-fold dosage range can be given.

FIG. 2. COMPARISON OF MYDRIATIC EFFECT ATTAINED WITH DIFFERENT DOSES AT THE SAME TIME AFTER INJECTION



Log-dose/effect curves for atropine, E3 and P10 on the mouse-eye. Abscissae = log-dose in g. Ordinates = mean diameter (in arbitrary units) of pupil 15 minutes after injection.

Results

Some 50 synthetic esters of the general type mentioned above were prepared in collaboration with Dr. A. H. Ford-Moore in the Dyson-Perrins Laboratory, Oxford, and tested in this Department by Dr. Edith Bulbring and Mrs. Izabella Wajda. Table I gives the results obtained with compounds modelled on benzilylcholine (Cl), in which the nature of the alkyl groups attached to the nitrogen atom was varied, the

relative potencies are recorded as potencies per mol in terms of atropine sulphate = 100. The most active compound (E3) has a molecular weight very close to that of atropine sulphate, and on a weight-for-weight basis is equal in activity to atropine, indeed, the log-dose mean-effect curve for E3 coincides with that for atropine (Fig. 2).

TABLE I. COMPARISON OF COMPOUNDS MODELLED ON BENZYLCHOLINE

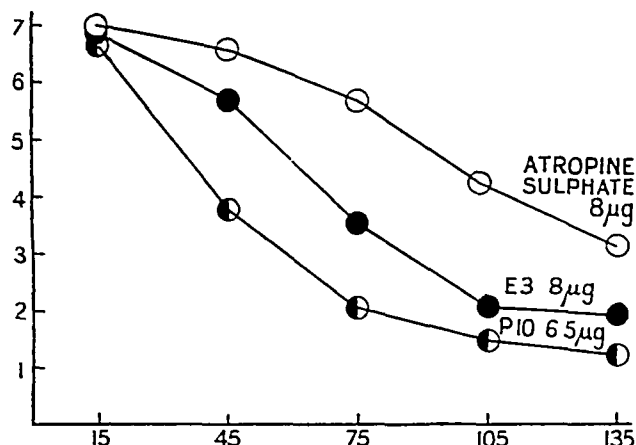
$(C_6H_5)_2C(OH)COOCH_2CH_2NR'R''\}X$					Relative potency per mol (atropine sulphate = 100) on the mouse eye	Number of mice used for substance and for atropine	
Serial number	R	R'	R''	X			
Cl	CH ₃	CH ₃	H	Cl	12.6	15	15
Cl	CH ₃	CH ₃	CH ₃	Cl	31	50	65
E3	CH ₃	CH ₃	C ₂ H ₅	Cl	104.4	60	90
E4	CH ₃	CH ₃	<i>n</i> -C ₃ H ₇	Cl	92.5	60	70
E5	CH ₃	CH ₃	<i>n</i> -C ₄ H ₉	Br	22	24	20
E6	CH ₃	CH ₃	C ₂ H ₅	Br	28	20	20
E7	CH ₃	CH ₃	<i>n</i> -C ₄ H ₉	Br	10.5	25	20
E11	CH ₃	CH ₃	<i>n</i> -C ₈ H ₁₇	Br	13	28	35
E1	C ₆ H ₅	C ₆ H ₅	H	Cl	6	25	50
E2	C ₆ H ₅	C ₆ H ₅	CH ₃	Cl	64	55	55
E14	C ₆ H ₅	C ₆ H ₅	C ₂ H ₅	Br	83	85	85
E15	C ₆ H ₅	C ₆ H ₅	<i>n</i> -C ₃ H ₇	Br	22	60	65

E3 differs from benzilylcholine chloride (Cl) only in the replacement of one methyl group on the nitrogen atom by ethyl, a change which trebles the activity. Another mydriatic choline ester, viz. di-*n*-butylcarbamylcholine chloride, was described by Swan & White in 1944, and it is interesting to note that the most active member of this class of compounds, viz. dibutoline, is also the one in which one methyl group of the choline ester is replaced by ethyl (Swan & White, 1944, 1945).

In comparing mydriatics it is important to distinguish between the intensity and the duration of the effect. The intensity of mydriasis (dilatation per unit dose) produced by E3 is equal to that of atropine in the mouse, but the duration of the effect is less. In Fig. 2 the mean diameter of the mouse-pupil, measured at 30-minute intervals, is plotted as a multiple of its normal size against time for both atropine and E3. It will be seen that the effect of E3 declines more rapidly than that of atropine.

The durations of mydriasis produced by E3 and atropine were also compared by local administration of one drop of 1% solutions twice daily into the eyes of cats. Atropine maintains full dilatation of the cat's pupil during five days of such treatment and for five days after administration has ceased. E3 showed little cumulative effect, some constriction of the pupil to light occurred each morning during the treatment and complete recovery was observed 24 hours after administration had ceased.

E3 was also tested by Professor Ida Mann on monkeys for paralysis of accommodation, which it was found to produce. It has since been used on human patients in the Oxford Eye Hospital and elsewhere with success. Although its effects are less prolonged than those of atropine, full dilatation and paralysis of accommodation can be maintained by more frequent administration. E3 also has the advantage that it

FIG 3 COMPARISON OF MYDRIATIC EFFECT AT DIFFERENT TIMES AFTER INJECTION OF STANDARD DOSES

Dilatation/time curves for atropine E3 and P10 on the mouse-eye
 Abscissae = time in minutes after injection
 Ordinates = multiple of normal pupil-diameter

can be used with safety on patients who are allergic to atropine and other belladonna alkaloids, no well-authenticated case of E3 irritation has so far been reported to the author. It can be used, like atropine, in 1% solution.

E3 is a white crystalline substance, readily soluble in water, and its solutions are neutral and stable to prolonged boiling. It is rapidly hydrolysed in alkaline solutions.

Toxicity E3 was tested for toxicity on mice and cats. In mice the LD_{50} was determined by three routes, and the figures for E3 and atropine are recorded in Table II.

TABLE II TOXICITY OF E3 AND ATROPINE COMPARED

Drug	Intra peritoneally	Subcutaneously	Orally
E3	0.8	3.2	20.0
Atropine sulphate	6.4	15.0	15.0

LD_{50} for mice (mg per 20 g)

No figure for the lethal dose in cats has been obtained, but the toxic symptoms produced by E3 and atropine have been compared. Atropine in a dose of 60 mg per kg subcutaneously produced severe tremor, rapid respiration (120 per minute) and vomiting, a state of severe excitement developed, followed by violent convulsions which ceased after six hours, the animal then appeared to be exhausted and unable to stand, the legs being spastic. The cat recovered and showed no symptoms except maximal mydriasis on the following day.

The symptoms produced by the same dose of E3 were different, during the first 15 minutes slight tremor appeared, the respiration quickened to 65 per minute and the cat gradually went to sleep. When aroused it appeared confused and could walk only with difficulty. After 2 hours it began to wake up and after 5 hours it could walk, although it was still sleepy. Next day no symptoms except mydriasis were

observed. A smaller dose (30 mg per kg) produced sleepiness and slight ataxia but, except for mydriasis, no other symptoms. The toxic symptoms of E3 in the cat are therefore less severe than those produced by atropine and are more like those recorded for scopolamine.

Other atropine-like properties E3 was also tested for other atropine-like properties. It reduced the contractions of isolated rabbit intestine produced by acetylcholine by the same amount as equal doses of atropine. It antagonized acetylcholine in the isolated and perfused cat's heart (Langendorff's preparation). The inhibition produced in this preparation by acetylcholine is abolished or reduced by 0.02-1.0 µg atropine. The reductions produced by E3 and atropine in equal doses were found to be identical, but the effect of E3 was shorter, being about half as long as that of atropine.

E3 also resembled atropine in antagonizing the salivary secretion produced by pilocarpine and carbamylcholine. Most of the substances listed in Table I were tested by Mr G S Dawes on the salivary gland of the cat by a method already described by Bülbring & Dawes (1945).

A steady flow of saliva, recorded by a Gaddum drop-timer, was produced in a cat under pentobarbitone by a slow intravenous infusion of carbamylcholine (0.004%) in Ringer-Locke solution, as this substance lowers the blood-pressure, adrenaline (0.002%) was also included in the infusion. The rate of infusion, which must be kept constant, was about 0.5 ml per minute. Atropine sulphate in intravenous doses of 1.5 µg produced a graded inhibition of the salivary flow and a corresponding rise of blood-pressure, and it was found possible to match both these effects with doses of the synthetic mydriatics. The relative potencies were estimated throughout by measuring the maximum effect of an injection.

The results are recorded in Table III in which the relative potencies per mol are expressed in terms of atropine sulphate = 100, standard deviations are given for the salivary-gland figures, and the relative molar potencies on the mouse-eye are included in order to facilitate comparison.

Inspection of Table III will show that the synthetic mydriatics have a more powerful effect on the salivary gland than on the blood-pressure (relative to atropine) and that several of them are considerably more potent than atropine on both, but in general the more powerful mydriatics are also the more potent in their effects on the salivary gland and the blood-pressure. A few substances, however, notably C1 and E2, which are less active than atropine on the pupil of the

TABLE III RELATIVE POTENCIES PER MOL IN TERMS OF ATROPINE SULPHATE (= 100)

Serial number of substance	Salivary gland (cat)	Blood pressure (cat)	Eye (mouse)
C4	11 ± 1.8	10	12.6
C1	196 ± 32	103	31
E3	258 ± 38	182	104.4
E4	293 ± 59	238	92.5
E5	147 ± 46	98	22
E6	—	—	28
E7	75 ± 19	63	10.5
E11	71 ± 36	32	—
E1	18 ± 4.6	21	13
E2	273 ± 49	239	6
E14	273 ± 44	190	64
E15	135 ± 30	78	83
			22

mouse, are considerably more active than atropine on the salivary gland of the cat

Quaternary Salts as Mydriatics

One of the interesting conclusions which can be drawn from the study of these synthetic mydriatics is that the salts of tertiary bases are invariably less active in their atropine-like properties than the corresponding quaternary metho salts, thus inspection of Tables I and III will show that C4 was less active than C1, and E1 less active than E2. Several other examples of the same relationship were encountered and consequently it appeared of interest to re-examine the quaternary metho salts of the belladonna alkaloids.

Crum Brown & Fraser (1868-69) were the first to examine the pharmacology of atropine methiodide and methosulphate. They found that both metho salts retained the mydriatic and vagal actions of atropine undiminished, but that the effects on the central nervous system were absent; both salts displayed a powerful curare-like action. Issekutz (1917) found atropine methobromide to be more active than atropine on the frog's heart and on the salivary gland of the rabbit, but about equal to atropine on the pupil. Cushny (1920) concluded that this salt was about 50% stronger than atropine in antagonizing pilocarpine in the dog's salivary gland. More recently Nyman (1942, 1943) reported that atropine methonitrate was about twice as active as atropine in antagonizing the salivary secretion produced by pilocarpine in man, but only about 25% more active than atropine in the human eye. *l*-Hyoscine and its metho salts showed less striking differences. Bulbring & Dawes (1945) found that the metho salts of atropine, *l*-hyoscyamine and *l*-hyoscine were each about twice as active as their parent alkaloids on the salivary secretion and blood-pressure of the cat.

The mydriatic activities of atropine methonitrate, *l*-hyoscyamine methiodide, *l*-hyoscine methiodide and eucatropine methiodide were compared with those of their parent tertiary bases in the eye of the mouse and of the cat, and the results are collected in Table IV. The relative mydriatic

TABLE IV TERTIARY AND QUATERNARY BASES COMPARED

Substance	Relative potencies per mol (atropine sulphate=100) on the eye of the			
	Mouse intraperitoneally	Number of mice	Cat locally	Number of cats
Atropine sulphate	100	—	100	—
Atropine methonitrate	228	30	50-100	9
<i>l</i> -Hyoscyamine sulphate	185	85	200	2
<i>l</i> -Hyoscyamine methiodide	492	60	100	2
<i>l</i> Hyoscine hydrobromide	491	75	1,000-1,500	9
<i>l</i> -Hyoscine methiodide	479	35	330	3
Eucatropine hydrochloride	0.4	30	0.05	7
Eucatropine methiodide	2.8	30	0.04	2

activities of these pairs of tertiary and quaternary bases depend upon the method of administration, thus atropine and *l*-hyoscyamine are more active than their respective metho salts when instilled into the conjunctival sac of the cat, but less active than the metho salts when injected into

the peritoneal cavity of the mouse. *l*-Hyoscine and its methiodide were equally active in the mouse, but *l*-hyoscine was about 3-4 times more active in the cat. Eucatropine was less active than its methiodide in the mouse but about equal to it in the cat.

The results in the mouse suggest that, except for *l*-hyoscine, the metho salts are intrinsically more powerful mydriatics than the tertiary bases, but that their relative weakness on local application to the cat's eye is due to relatively poor absorption from the conjunctival sac. When these results are taken in conjunction with those of other workers briefly outlined above, the conclusion is inescapable that the metho salts of the belladonna alkaloids are intrinsically more powerful antagonists of acetylcholine than the tertiary bases, and the same conclusion applies *mutatis mutandis* to the synthetic benzilic esters discussed above.

The Benzilic Acid Analogue of Eucatropine

It will be noticed in Table IV that eucatropine is a very feeble mydriatic relative to atropine. Eucatropine is a mandelic ester (see formulae above) and the replacement of the H-atom on the α -C-atom of the mandyl group yields the corresponding benzilic ester, the hydrochloride of the latter substance (P8) was 35 times as active as eucatropine in the eye of the mouse. Similarly the methochloride (P10) was 60 times as active as eucatropine methiodide. P10 was 70% more active than atropine sulphate on a molar basis and 20% on a weight basis, but it proved to be less satisfactory than E3 in human eyes, probably because its mydriatic action wears off rapidly (Fig. 2), moreover, like eucatropine, it is not a cycloplegic. The figures quoted above, however, show in a striking way the peculiar efficacy of benzilic acid as the esterifying acid in mydriatic esters of amino-alcohols.

Conclusion

The practical outcome of the work described herein was the discovery of a synthetic mydriatic, benzilyloxyethyl dimethylethylammonium chloride, which has been referred to so far as E3, but which it is proposed to name lachesine (from *λαχσις*, one of the Fates whose sister *ατρος* gave her name to atropine). Clinical reports on lachesine by Mann (1946) and Riddell (1946) have been published. While it is unlikely that lachesine will replace atropine in normal times, it may well prove to be a valuable addition to the armoury of the ophthalmic surgeon both as a short-acting mydriatic and cycloplegic and for the treatment of patients who are allergic to the belladonna alkaloids. Full details of the chemical and pharmacological work on lachesine and other synthetic substitutes for atropine have been published or are in course of publication (Ing, Dawes & Wajda, 1945, Ford-Moore & Ing, 1946).

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THE MAINTENANCE OF BLOOD-PRESSURE IN ANAESTHESIA

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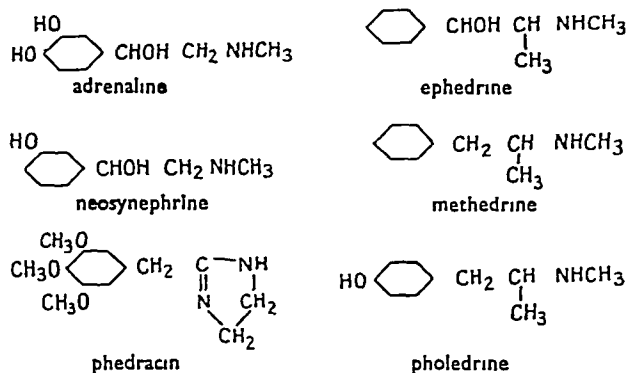
The blood-pressure is normally controlled by impulses proceeding from the vasomotor centre in the medulla by way of the preganglionic and then the postganglionic sympathetic fibres to the blood-vessels, the impulses constrict the blood-vessels and so raise the pressure inside them. When a spinal anaesthetic is given the blood-pressure usually falls to a varying extent as the anaesthetic diffuses upwards in the spinal fluid and blocks the conduction in the preganglionic fibres. To restore the blood-pressure it is clear that a pressor agent which acts peripherally must be used, no effect will be exerted on the calibre of the vessels by a substance which stimulates the vasomotor centre.

Mode of Action of Ephedrine

The best-known substance which acts directly on the vessels is adrenaline. It cannot, however, be used to restore the blood-pressure because its action is transient, and it is also violent. A more suitable substance would be one which exerted a prolonged effect and which acted less abruptly. In 1927 Rudolf & Graham introduced ephedrine, and their paper was closely followed by that of Ockerblad & Dillon. It is worth while to consider the mode of action of ephedrine, as it sheds light on the action of other substances which were introduced later. The formulae of adrenaline and of ephedrine are given in Fig 1, to the general similarity of these it was formerly thought that ephedrine owed its pressor action. Thus it was supposed that adrenaline was structurally designed to combine with a cell receptor of a special type, and that the similar though feebler action of ephedrine was explained by its approximation to this structure. This view has now been greatly modified as a result of a series of observations.

Ephedrine was found to have very little vasoconstrictor action on the vessels of the frog perfused with Ringer's solution (Schaumann, 1928), or of the dog's leg perfused with defibrinated blood (Burn, 1932). A vasoconstrictor action appeared only when adrenaline was added to the blood. These were peculiar findings, since they seemed illogical. If a substance such as ephedrine has a vasoconstrictor action, this action would be expected to be greatest in the absence of all other vasoconstrictor agents, certainly the presence of adrenaline would be expected to diminish its action, and not to augment it. Why was the action of ephedrine greater in the presence of adrenaline?

FIG 1 FORMULAE OF PRESSOR DRUGS INVESTIGATED



It was shown that ephedrine inhibits the action of amine oxidase (Blaschko, Richter & Schlossmann, 1937), an enzyme present in animal tissues, which destroys adrenaline. The theory was therefore put forward by Gaddum (1938) that the action of ephedrine in the body was to reduce the rate of destruction of adrenaline. If we suppose that adrenaline is secreted into the blood-stream by the suprarenal glands, and that it is being steadily destroyed by tissue enzymes, it is evident that if ephedrine inhibits the action of these enzymes, the effect of ephedrine will be to raise the concentration of the adrenaline in the blood. Many observations indicate that a large part of the action of ephedrine is to be explained in this way.

Thus the greater vasoconstrictor effect of ephedrine in the presence of adrenaline is explained by supposing that ephedrine itself is a very poor vasoconstrictor, but that when adrenaline is present, and is being continuously destroyed by tissue enzymes, the injection of ephedrine diminishes its rate of destruction and thus causes vasoconstriction by raising the concentration of adrenaline.

The remaining part of the action of ephedrine is probably explained by the former view that its structural similarity to adrenaline enables it to combine with the cell receptors with which adrenaline combines, thus ephedrine augments the rate and force of the isolated heart perfused with Ringer's solution without requiring the presence of adrenaline to exert this effect.

This account makes it likely that the action of any substance having a structure in part similar to that of adrenaline will be due to two effects: the substance will compete with adrenaline for enzymes which destroy adrenaline, and by so doing reduce the rate of adrenaline destruction; the substance will also excite certain tissues directly which are ordinarily excited by adrenaline. The extent to which the one or the other of these actions predominates will differ according to the structure of the substance.

Some Other Pressor Compounds

After the introduction of ephedrine, Kuschinsky & Oberdisse (1931), working in the laboratory of Paul Trendelenburg, described the properties of *meta*-sympatol, since known in the United States as neosynephrine. Except that the -OH group in the *para* position in the benzene ring is missing, neosynephrine is identical in structure with adrenaline. In 1937 Rein introduced veritol, now known in Britain as pholedrine. Phedracin was introduced in 1938, it is not a near relation of adrenaline. Finally methedrine, known in Germany as pervitin, and closely related to amphetamine (which has the proprietary name benzedrine), was described in this country by Dodd & Prescott in 1943 (see Fig 1).

All these compounds are pressor. Their action is easily demonstrated by injecting any of them into the vein of a cat in which the medullary centres have been depressed by successive doses of pentobarbitone so that the blood-pressure is reduced to about 50 mm Hg and respiration is maintained artificially. If the therapeutic dose, for a man, of one of these pressor substances is calculated per kg body-weight, and if this dose is injected into the cat, there is a large rise of blood-pressure which, after reaching a peak, declines at a rate which varies according to the substance injected.

Action of Pressor Drugs on the Heart

As a prelude to the investigations to be described, a series of experiments was carried out to determine what doses of the different substances produced the same rise of blood-pressure in the spinal cat. An investigation was then made of the mode of action of these substances to see how they differed (Elmes & Jefferson, 1942). Their action was first examined on the isolated heart of the cat perfused through the coronary vessels with warm oxygenated Ringer's solution (Methedrine was not examined in this way). Each substance was injected at a given moment into the fluid going to the heart, and the doses of the different substances were chosen to be in the same ratio as the doses having the same action on the blood-pressure.

The effect of ephedrine, pholedrine and neosynephrine on the heart-rate is shown in Fig 2. The figure, which represents the mean of more than 100 observations with each

FIG 2 EFFECTS OF PRESSOR SUBSTANCES ON THE RATE OF THE HEART-BEAT

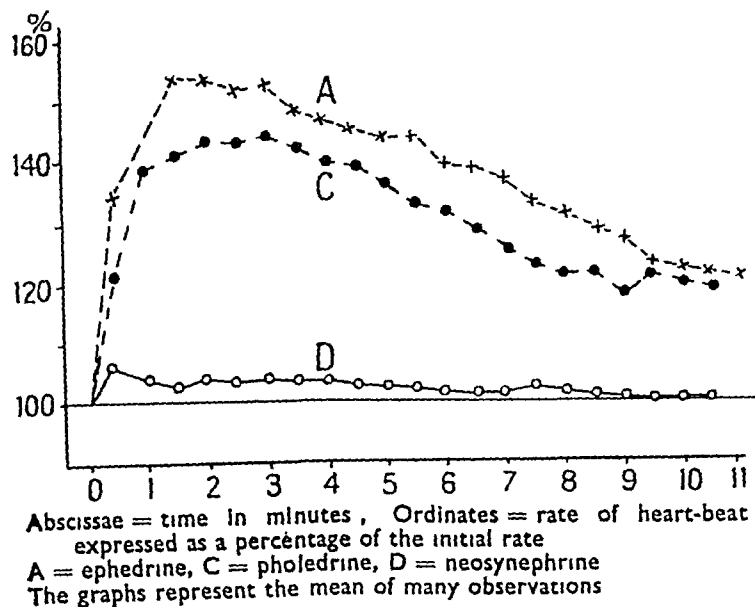
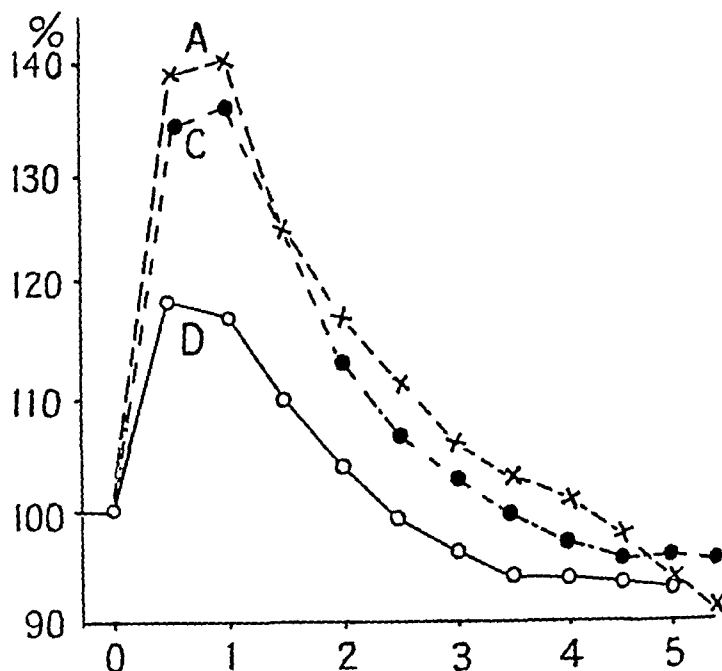


FIG 3 EFFECTS OF PRESSOR SUBSTANCES ON THE AMPLITUDE OF THE HEART-BEAT



Similar observations to those in Fig 2, but the ordinates = amplitude of the contractions expressed as a percentage of the initial amplitude

A = ephedrine, C = pholedrine, D = neosynephrine

substance, shows that both ephedrine and pholedrine increase the heart-rate, the effect of ephedrine being a little greater than that of pholedrine, while neosynephrine has almost no effect on the heart-rate. The effect of ephedrine and pholedrine is prolonged. This evidence that neosynephrine does not increase heart-rate constitutes an important advantage over ephedrine and pholedrine.

The effect of these substances on the amplitude, that is in increasing the force of the beat, is shown in Fig 3. Here again it is evident that both ephedrine and pholedrine owe a larger part of their action on the blood-pressure to stimulation of the heart than does neosynephrine. Phedracin was found to exert very little effect on the isolated heart, even when injected into the fluid passing through the coronary arteries in very large dose.

Action of Pressor Drugs on the Blood-vessels

The action on blood-vessels was determined by injecting the substances into the Ringer's solution which was perfusing the vessels of the rabbit's ear. It was also determined in the vessels of the dog's hindleg perfused with blood. The first conclusion which could be drawn was that neosynephrine and phedracin possessed a vasoconstrictor action which was regularly demonstrable, their action stood in contrast to the action of ephedrine and of pholedrine, these latter substances caused vasoconstriction in some preparations but not in others, even in large dose.

Evidence that ephedrine acts not as a direct vasoconstrictor substance, but by potentiating the effect of adrenaline, has already been described, and the present observations show that this is true of pholedrine as well. The second conclusion was that the constrictor action of both neosynephrine and phedracin plays the major part in causing the rise of blood-pressure which follows their injection. Doses of neosynephrine and of phedracin which caused equal rises

of blood-pressure were in the ratio 1 to 14. Doses which caused equal vasoconstriction were in the ratio 1 to 10. It may be noted, by the way, that, because neosynephrine has this vasoconstrictor action, Tainter & Stockton (1933) suggested that it might be used instead of adrenaline with local anaesthetics, such as procaine, to prolong their action. Elmes & Jefferson (1942) therefore tested ephedrine, pholedrine, neosynephrine and phedracin for this purpose, injecting mixtures of each with procaine into the skin of guinea-pigs to determine the duration of anaesthesia. It was found that neosynephrine alone was effective and that, curiously enough, phedracin was ineffective despite its predominantly vascular action.

The results of examining the effect of the 4 substances on the vessels of the rabbit's ear were confirmed when the vessels of the dog's hindleg, perfused with defibrinated blood, were used as the test-object. In Table I the doses of the 4 substances having similar effects are shown.

It is probable that the effects of the 4 substances on the blood-pressure depend on other effects as well as on a direct action on the heart and on the vessels. Thus Rein (1937) attributed the pressor effect of pholedrine to a rise in tonus

TABLE I EQUIPOTENT DOSES OF PRESSOR COMPOUNDS

	Action on blood pressure	Action on heart	Action on vessels
	mg/kg	μg	μg
Ephedrine	2.65	15.0	60.0*
Neosynephrine	0.15	1.25	0.25
Pholedrine	0.76	5.0	12.0*
Phedracin	2.05	—	2.5—18.0

* In many experiments these substances were inactive on the vessels.

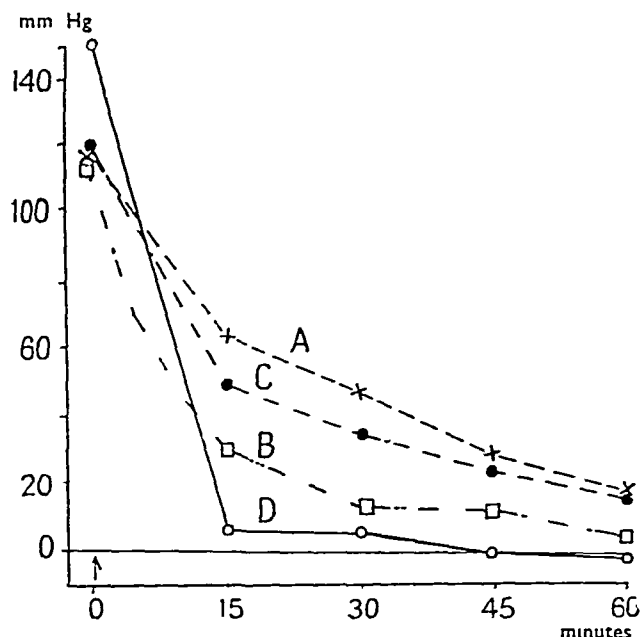
on the venous side of the circulation, in particular to a reduction of spleen- and liver-volume. In confirmation of this view, Chakravarti & Tripod (1940) found that pholedrine caused a striking diminution of the isolated and perfused dog's liver, a much greater diminution than was caused, for example, by ephedrine. It is likely that the pressor action of phedracin also depends on other effects than those examined, for it was found to have almost no action on the isolated heart, and to vary greatly from one preparation to another in its action on the vessels, sometimes only a large dose exerted a constrictor action.

The Restoration of the Blood-pressure

To choose the most suitable substance to restore the blood-pressure it is necessary to know for how long the effect of a substance lasts, a substance with a relatively transient action will be of less value. A comparison of the 4 compounds was made, in which each was tested in five cats, and the mean result was calculated. The comparison was made under the conditions described above, in which large doses of pentobarbitone had been given so that the blood-pressure was about 50 mm., and respiration was maintained artificially.

The results are shown in Fig 4. The effect of neosynephrine was the soonest over. In 15 minutes after the injection the blood-pressure was back to within a few millimetres of the level before injection. The effect of ephedrine lasted longest, and that of pholedrine was almost as long.

FIG 4 DURATION OF PRESSOR EFFECT OF A SINGLE INJECTION



Shows the fall of the blood pressure from the peak after a single injection.

The ordinates represent the height of the blood pressure above the initial level.

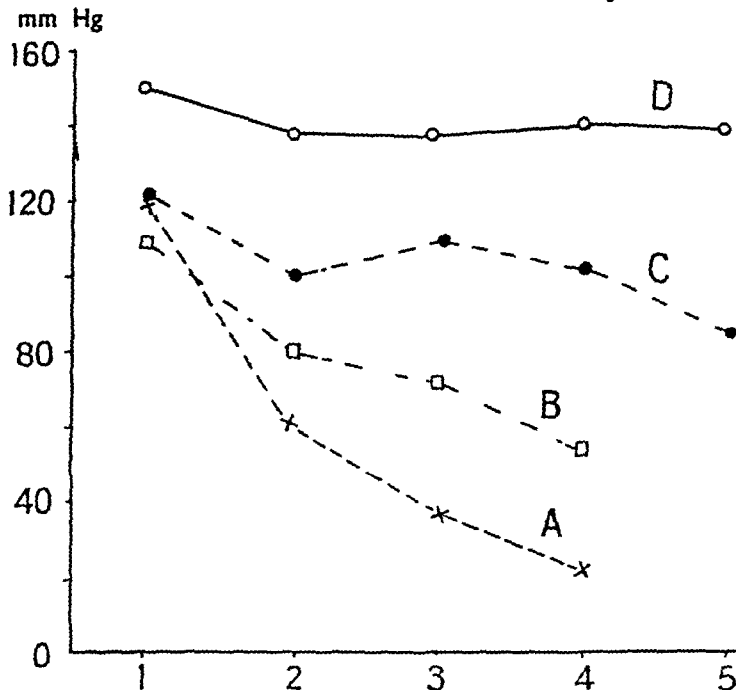
A = ephedrine B = phedracin C = pholedrine and D = neosynephrine.

Each graph is the mean of observations in 5 cats.

After an injection of ephedrine the blood-pressure was about 30 mm. higher than before injection, at 45 minutes, and about 20 mm. higher at 60 minutes. Thus, for a lasting effect, ephedrine was the best of the 4 substances.

When the blood-pressure has fallen, it is likely that more than one injection of the restorative agent will be required in the course of a few hours, even when the longest-acting substance is used. It is therefore important to know, when a substance is selected, that it will produce a good effect in later injections than the first. To examine this point, each of the substances was injected at hourly intervals for 4 hours, and the mean rise of blood-pressure was determined for each substance. The results are shown in Fig 5. Here it is seen that the effect of neosynephrine remains exactly the same at each injection, whereas the effect of ephedrine becomes less and less. An injection of ephedrine, which when given for the first time caused the pressure to rise 120 mm., caused the blood-pressure to rise by about 25 mm. when given for the fourth time. Of the other two substances, pholedrine maintained its effect on repeated injection better than phedracin, the fifth injection of pholedrine produced a rise of 90 mm. At this point of the investigation it therefore appeared that, of the 4 substances, pholedrine was the most useful. The effect of an initial injection of pholedrine lasted almost as long as that of ephedrine, and the effect of subsequent injections of pholedrine was much better than that of subsequent injections of ephedrine.

An examination of the changes in the level of the blood-

FIG. 5 PRESSOR EFFECTS OF REPEATED INJECTIONS

Shows the extent of the rise of blood-pressure when injections were made at hourly intervals

Abscissae = hours at which injections were made

Ordinates = mean rise of blood-pressure

D is the graph for neosynephrine and shows that the rise is just as great after the fifth injection as after the first

C = pholedrine, B = phedracin, A = ephedrine

pressure during the course of the experiments, however, revealed a difference in the effect of the different substances which is not seen in the analysis so far. When experiments in which neosynephrine was injected were considered, it was seen that there was no rise in the blood-pressure except at the times when the injections were made and for about 15 minutes afterwards. Apart from these rises of short duration there was no general rise. The mean blood-pressure before the first injection of neosynephrine was 47 mm, the mean blood-pressure before the fifth injection was 43 mm. So far as phedracin and pholedrine were concerned the situation was rather better (see Fig. 6). The mean blood-pressure before the first injection of phedracin was 58 mm, but before the fourth injection it was 66 mm, thus, during the course of the experiments with phedracin, there was an upward tendency indicating that its effect was persisting all the time. The results with pholedrine were similar to those with phedracin.

The results with ephedrine were more definite. Before the first injection the blood-pressure was 53 mm, before the second it was 72 mm, before the third it was 75 mm, and before the fourth it was 87 mm. Thus, the restorative action of ephedrine was seen to be decidedly greater than that of the other substances, for the general level of the blood-pressure between the injections is of more consequence than its height just after injection.

Results with Methedrine

The work so far described was carried out by Elmes & Jefferson and a brief account appeared in their paper published in 1942. The work of Dodd & Prescott on methedrine appeared in 1943. These workers recorded the blood-pressure and pulse-rate in patients every 3-5 minutes in 130

operations, "and in 54 of these the systolic pressure or the pulse-pressure dropped sufficiently for the patient to need a pressor agent. Methedrine was used when the systolic pressure fell to 80 mm or less, 20 minutes was allowed, first, for natural recovery." They found that out of the 54 cases given methedrine, only one failed to respond to it. In the others the blood-pressure was restored to a normal level in a period of from 2-18 minutes. It was administered either intravenously or intramuscularly or both. The dose for a single intravenous injection was 10-20 mg, and a single intramuscular injection 15-30 mg. When both injections were given, the doses were 10-15 mg intravenously and 15-20 mg intramuscularly. In 44 out of the 54 cases only one injection was necessary. They were impressed by the pressor action of methedrine which is "sustained over a period of several hours after the operation." Extrasystoles were noted in three patients, but these were also observed in patients to whom methedrine was not given. Dodd (Dodd & Merton, 1939, Dodd, 1940, 1942) had previously investigated the action of ephedrine and pholedrine, and was therefore able to compare methedrine with them. Dodd & Prescott say that methedrine is superior because it does not cause a rapid rise and fall of blood-pressure, because its effect lasts for several hours and not for 30-45 minutes, and because one injection is usually enough.

In view of these results, which speak so much in favour of methedrine, a series of observations were made in cats, in which methedrine was compared with pholedrine. Eight cats were used to observe the effect of methedrine and 4 were used for pholedrine. Both methedrine and pholedrine were given in a dose of 0.35 mg per kg, which is approximately equivalent to 20 mg for a man (of 60 kg). The mean initial rise of pressure caused by the two substances was about the

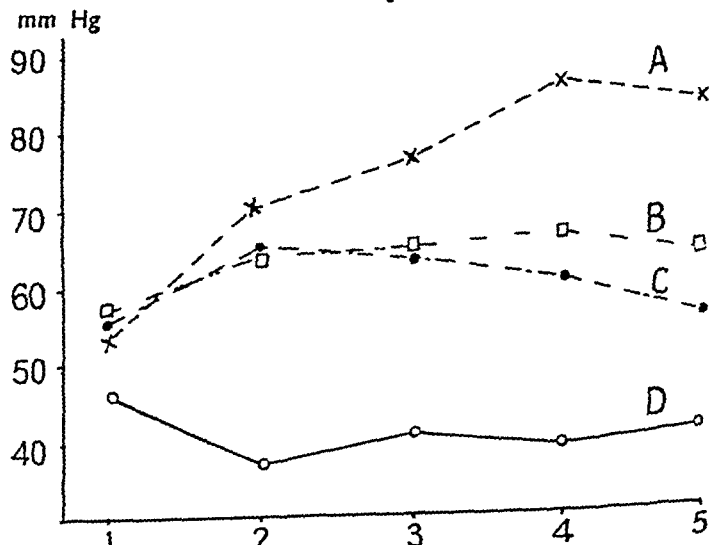
FIG. 6 PERSISTENCE OF PRESSOR EFFECT WITH SEVERAL INJECTIONS

Chart showing the level of the blood-pressure immediately before each of the successive injections of the pressor agents

Abscissae = hours before which injections were made

A = ephedrine, B = phedracin, C = pholedrine, D = neosynephrine

Note that with neosynephrine there was no rise in pressure throughout the course of the experiment. Note that with ephedrine each injection left the blood-pressure much higher one hour later, so that there was a steady rise throughout. The results with methedrine (not shown) were exactly the same as those with ephedrine.

same (91 mm for methedrine, 94 mm for pholedrine) The other effects suggested that the difference between methedrine and pholedrine was very similar to the difference between ephedrine and pholedrine, and that methedrine and ephedrine resembled one another closely Just as later injections of pholedrine had more pressor action than later injections of ephedrine, so they had more pressor action than later injections of methedrine The mean rises for 4 successive hourly injections were, for pholedrine, 94, 65, 60 and 63 mm For methedrine they were 91, 50, 42 and 52 mm

Likewise methedrine caused the general level of the blood-pressure to rise throughout the experiment, just as did ephedrine, and almost to the same extent Thus the initial blood-pressure before the first injection of methedrine was a mean figure of 56 mm, before the second it was 71 mm, before the third it was 82 mm, and before the fourth it was 92 mm These figures almost coincide with the figures for ephedrine given in Fig 6, and show that there is a close similarity between the action of the two substances This is to be expected from their structural relationship, for methedrine can also be called desoxyephedrine

The studies on the cat thus point to the conclusion that the best substances for restoring the blood-pressure in anaesthesia are methedrine and ephedrine, and that these are both superior to pholedrine, phedracin and neosynephrine for this purpose In view of the positive statement of Dodd & Prescott (1943) that in patients methedrine is superior to ephedrine, it is desirable that these substances should be carefully compared in a series of cats before any suggestion is made that ephedrine is not inferior to methedrine

Use of a Pressor Agent in Anaesthesia

In the operations in which Dodd & Prescott made their observations the anaesthetics employed were of all kinds—spinal, general (including gas and oxygen, ether and trichlorethylene), local anaesthetics and intravenous pentothal They remark that "a fall in blood-pressure usually, though not always, occurs after giving a spinal anaesthetic Pressor agents are often given prophylactically to prevent this, but we preferred to correct the fall if and when it occurred" They further say "If the spinal anaesthetic does not bring about a fall in blood-pressure and a pressor agent is administered, the resulting rise in blood-pressure causes increased haemorrhage from the operation wound" These words appear to be worth emphasis

Pressor Substances by Intravenous Drip

Some workers recommend that, to maintain the blood-pressure during anaesthesia, adrenaline should be given by intravenous drip When adrenaline is infused at constant rate into the vein of an anaesthetized cat or dog, it is observed that, unless great care is taken to maintain the rate of infusion constant, serious fluctuations in the blood-pressure may occur without warning A more important observation, however, is that, when an infusion of adrenaline is stopped, the blood-pressure may then fall very low Bülbring & Burn (1942) have shown that adrenaline, when present in the blood in low concentrations, facilitates the transmission of sympathetic impulses through the sympathetic ganglia When, however, the concentration of adrenaline is higher, the transmission is impaired and impulses from the vasomotor

centre fail to reach the blood-vessels, the blood-pressure remains good while the adrenaline continues to enter the blood-stream, but when it is stopped, there is complete vascular relaxation There will be a risk of this vasomotor collapse occurring at the end of intravenous adrenaline infusion

It may be that a safer agent for this purpose is neosynephrine, but the effect of administering it continuously has not yet been examined

Summary

The action of the substances ephedrine, neosynephrine, pholedrine, phedracin and methedrine in restoring a blood-pressure which has been depressed by the injection of large doses of pentobarbitone has been analyzed and their relative value has been indicated The evidence obtained in cats indicates that the best substances are methedrine (pervitin) and ephedrine

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THE VISUAL MEASUREMENT OF BLOOD-PRESSURE

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The determination of the systolic and diastolic pressures and, perhaps to an even greater extent, the determination of their difference—the pulse-pressure—form one of the anaesthetist's most important guides to the condition of his patient during an operation The customary method of determination by the aid of a stethoscope strapped to the arm of the patient has a number of disadvantages, not the least of which is that it is usually inaccessible beneath the sterile coverings which drape the patient. The manipulations of the surgeon may easily displace the stethoscope, unknown to the anaesthetist, and failure to hear the sounds properly may be attributed to this cause, when in fact they should be interpreted as a sign of a deterioration in the condition of the patient.

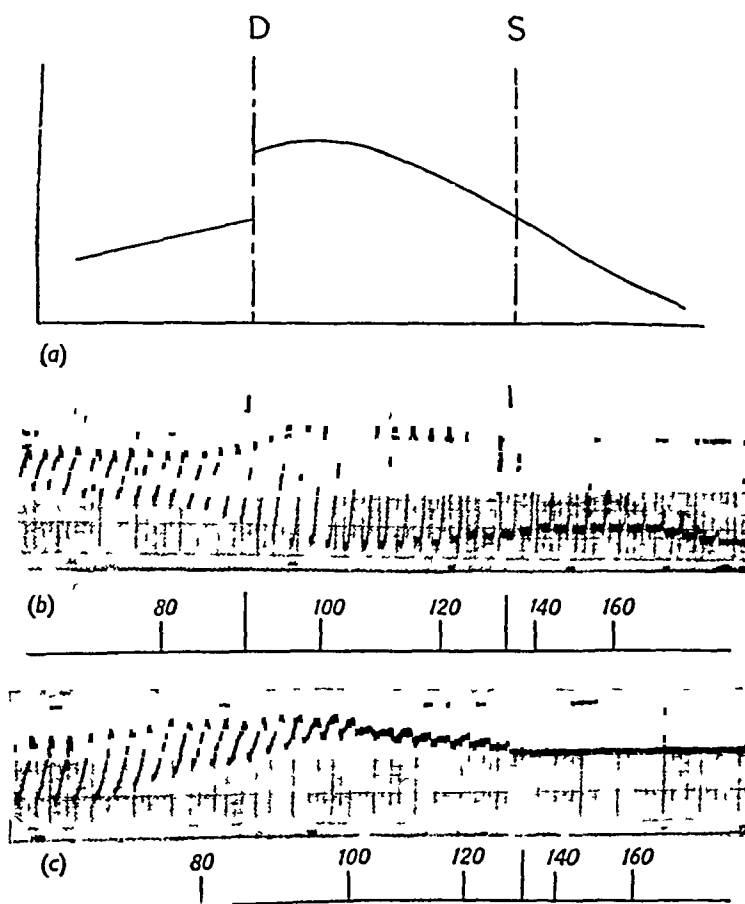
Further, the auscultatory method of blood-pressure determination may be rendered difficult and uncertain by the intrusion of small sounds due to any one of a multitude of causes

It is therefore clear that a visual record of, for example, the pulse-pressure would have considerable advantages, and if, in addition, this record could be arranged to be independent of the manipulations of the anaesthetist, it would have the further important advantage of leaving him free to devote all his attention to his patient at just those moments of crisis when it is most important for him to assess accurately the effects of his clinical procedures

General Approach to the Problem

In approaching the problem of the measurement of blood-pressure *de novo*, two main methods suggest themselves. The first is to employ the Korotkov sounds, the second to employ the pressure-pulsations taking place in an inflated cuff bound round a limb. Besides the practical objections to the use of the sounds which have already been advanced, there is the further difficulty that the significance of the various sounds in terms of the behaviour of the artery is by

FIG 1 COMPARISON OF PREDICTED AND ACTUAL RELATION BETWEEN AMPLITUDE OF PRESSURE-PULSATION AND DEGREE OF CUFF-PRESSURE



- a Theoretical curve
Abscissae = cuff-pressure (mm Hg) Ordinates = pressure-pulsations D = diastolic pressure S = systolic pressure
b Optically-registered diastolic record
c Optically-registered systolic record [The records should be read from right to left]

no means well understood. Moreover, the design of an instrument to make use of them would necessarily entail the use of electronic amplifying devices of one kind or another. The result would be, not only that the apparatus would be complicated and expensive, but also that it would depend for its working on outside sources of electrical supply.

The employment of the pressure-pulsations in a cuff seems to offer a simpler approach and to promise a final product of a less complicated and expensive type. It is true that oscillometers of various kinds are already on the market, but these are not entirely satisfactory because there is no indication of the physical or physiological significance of their readings or records except what can be deduced empirically by experimentation. As will be seen later, in many cases the deductions which have been made are fallacious.

Principles and Method Adopted

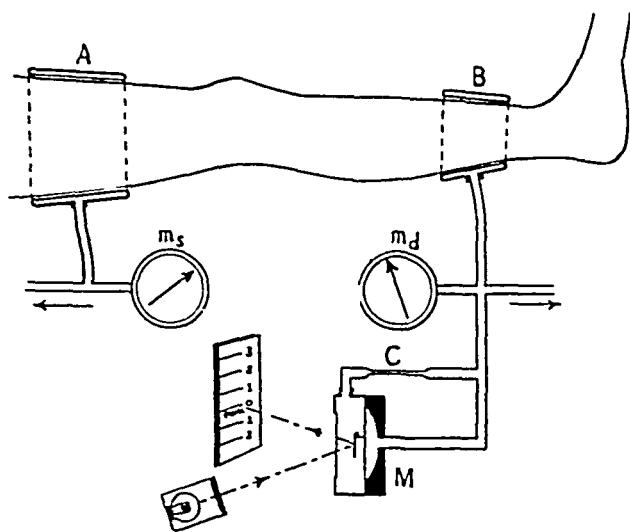
Our own approach (Evans & Mendelssohn, 1942) to the problem was from the standpoint of the first principles of physics which were applied to a simplified model of an artery as being an elastic tube surrounded by an incompressible jelly. We first made a simple analysis of the pressure-pulsations which would be observed in a cuff bound round the limb and inflated to various constant pressures. Our conclusions were as follows. If the external pressure exerted by the cuff is always greater than systolic pressure, i.e. if the cuff-pressure is above systolic, then the section of artery beneath the cuff will be occluded and no blood will flow. On the other hand, if the cuff-pressure is not too far above systolic, there will be small pressure-pulsations in the cuff due to the impact of the pulse-wave on the upper edge of the occluded section. Each wave will open the artery a little, but the depth of penetration of this "edge-effect" will be small. If, now, the cuff-pressure be lowered to a value intermediate between systolic and diastolic pressures then, during some part of each heart-cycle, the artery will be occluded, and during another part of the cycle the artery will be fully patent. For cuff-pressures in this region, therefore, the arterial volume-changes will be large, and these will lead to relatively large pressure-pulsations in the cuff.

Finally, if the cuff-pressure is below diastolic pressure, then at no time does the external pressure exceed the internal, and the only volume-changes which occur during the heart-cycle will be the small changes consequent upon the elastic response of the artery to the varying pressures within it. In this region the volume-changes, and consequently the pressure-pulsations in the cuff, will be small.

The predicted relation between the size of pressure-pulsation and the cuff-pressure is shown in Fig 1a. It will be noticed that the variation of size as the cuff-pressure crosses systolic pressure is continuous, whereas at diastolic pressure there is a sharp change, corresponding to the transition from an artery alternating between complete occlusion and complete patency above diastolic, to an artery undergoing small elastic pulsations below that pressure. A further conclusion from the analysis was that at any constant cuff-pressure below diastolic, the size of pulsation observed in the same patient should be proportional to the pulse-pressure in the artery.

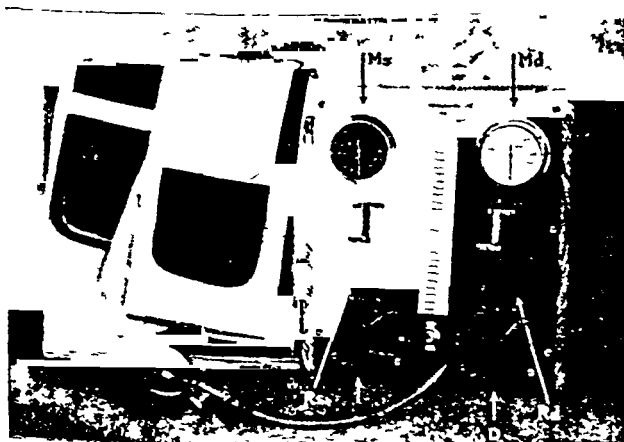
The Sphygmoscope and its Operation

The sphygmoscope which we developed was based on

FIG 2. SIMPLIFIED DIAGRAM OF THE SPHYGMOSCOPE

A = 2nd cuff used for determining systolic pressure
 B = detecting cuff M = membrane manometer
 C = capillary tube. m_d , m_s = aneroid manometers
 \longleftrightarrow = to inflators
 For description of principle and operation see text

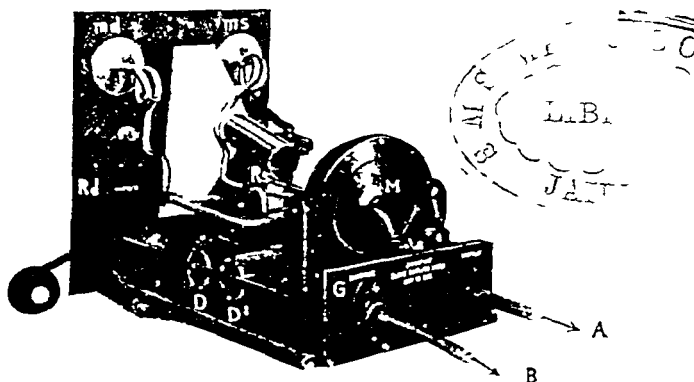
these principles. The principle of the method is illustrated in Fig 2. B is the cuff, the pulsations in which are to be detected and studied. The means of detection is a sensitive differential membrane-manometer, M, consisting of two chambers. The smaller of these is connected directly to the cuff, while the larger is connected to it through a capillary tube, C. The effect of this capillary is that pulsations are carried directly to the smaller chamber only, and are damped out in the capillary. On the other hand, the capillary transmits slow pressure-changes, due perhaps to changes of the fluid content of the limb, and keeps the pressures in the two chambers equal. The aneroid manometer m_d

FIG 3 SPHYGMOSCOPE, SHOWING CONTROL PANEL

m_s , m_d = aneroid manometers
 R_s , R_d = snap-action release-valves
 S, D = taps for systolic (S) and diastolic (D) records

indicates the mean pressure in the circuit, while the movements of the membrane in C are shown by means of a mirror and a light-beam and scale. The movements of the light spot on the scale indicate the size of the pressure-pulsations in B. These are of the order of a few millimetres of water at most, and hence high sensitivity of M is essential. The differential arrangement allows the detection of these small pulsations, since the membrane is not called upon to withstand any but the smallest of pressure differences. In the actual construction (Fig 4) a wide by-pass tap D^1 is provided which connects the two chambers of M and allows rapid inflation to any pressure without damage to the membrane. When this tap is open the manometer does not, of course, record pulsations. To allow the pressure to be lowered gradually during recording, the capillary C is divided into two parts, being tapped at the centre by a slow-release valve R_d with a snap action.

This part of the apparatus serves for the determination of diastolic pressure and the estimation by continuous registration of the pulse pressure. The method of operation is as

FIG 4 SPHYGMOSCOPE WITH OUTER CASE REMOVED

m_d , m_s = aneroid manometers
 R_d , R_s = snap action release-valves
 D = inflation tap linked to D^1

D^1 = by pass tap
 M = membrane manometer
 A, B = to cuffs A, B (compare Fig 2)

follows. This part of the apparatus (the detecting circuit) is inflated to any desired pressure above the expected diastolic, and the by-pass closed. The release valve is then opened and the size of pulsations observed. As the pressure falls the size of pulsations follows the curve of Fig 1a until, when diastolic pressure is reached, there is a sudden drop in size. At this point the release-valve is snapped shut and the pressure is read. Fig 1b shows an actual photographic record of this process, and it will be seen that the diastolic pressure is defined unambiguously, certainly within two or three mm of mercury either way.

For the estimation of pulse-pressure, the pressure in B is set to any desired value below diastolic, and then, this pressure being maintained, the size of the pulsations is proportional to the pulse-pressure, previously determined from separate observations of systolic and diastolic pressures.

For the determination of systolic pressure, the absence of any sharp change in the curve shows that a single cuff will be insufficient. A second cuff A (Fig 2), placed proximal to

the first, the pressure in which is indicated by the aneroid manometer m_1 , is employed. The role of B now becomes solely that of a detector of any blood-flow in the artery beneath it, and it is inflated to any convenient pressure below diastolic. If A is now inflated to a pressure above systolic, B will record nothing. As the pressure in A is allowed to fall to systolic, spurts of blood will begin to flow under A and will be detected by pulsations in B. In the actual construction, the inflation-tubes and manometers for the two circuits are housed in the same box (Fig 3, 4), and the reading is made by releasing A by means of a second snap-action release-valve, R_2 , which is snapped shut, and the pressure read, at the instant when the light-spot starts to pulsate. In Fig 1c a record of this is shown. The trace remains level until a pressure of about 132 mm is reached, at which point pulsations begin. By this arrangement all the edge effects are confined to cuff A and thus excluded from the record, and a sharp and unambiguous criterion of systolic pressure is secured.

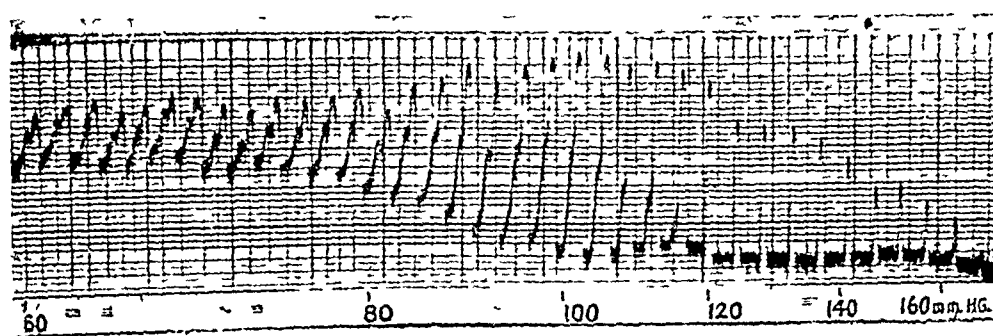
Some Criticisms Considered

Our method of solving a medical problem by means of a simple physical model and its mathematical interpretation is admittedly unusual, and it is not surprising that it has met with criticism from medical men (Macintosh, Cowan, Heller & Plesch, 1943) mainly turning on the question as to whether it is possible to secure an adequate representation by a necessarily much simplified model, of so complex a system as an artery pulsating in living tissues. The whole question is of fundamental importance and requires to be discussed in some detail, not only because of its importance for the problem of blood-pressure measurement, but also because of its bearing on the general problem of the application of physical methods to medical questions. In the present case, the most fundamental objection which could be offered would be that the theoretical formulae cannot be expected to yield definite criteria of systolic and diastolic pressures. Since the validity of these objections was discussed (Evans & Mendelssohn, 1943¹) on the basis of the visual observations, we have made photographic recordings by means of a sphygmoscope fitted with a camera.

Considering first the criterion for diastolic pressure (Fig 1b) the photographic record shows a distinct sudden decrease in the amplitude of pulsations at about 90 mm of mercury, and this decrease was found to coincide with the value of diastolic pressure determined by the accepted auscultatory method. This feature is present in all the recorded cases. The decrease is usually of the order of 50%, and only in a small number of cases, particularly in children, does it fall below 30%. Even in these, the diastolic criterion becomes unmistakable after a little experience.

¹ This communication also contains a list of references to previous work.

FIG 5 INFLUENCE OF RESPIRATION ON DIASTOLIC RECORD



The record shows a temporary increase in amplitude of the pressure-pulsations, presumably due to the effect of respiration in causing a brief rise in diastolic pressure. [Read from right to left.]

Another question which has been raised in this connection is that of the accuracy with which the pressure-criteria can be determined by this method. Arguments of this kind, however, usually ignore the fluctuation which the characteristic pressures continually undergo, particularly as a result of respiration. We shall return to this point later. At the moment it is only necessary to point out that our records show that the accuracy of measurement is determined *not* by the method of observation but by the extent of these natural fluctuations. We have, for instance, recorded cases (Fig 5) in which, after an initial fall in the amplitude of the pressure-pulsations a temporary rise occurred. This is due to a shift of the value of diastolic pressure by a few mm to a higher value (evidently as the result of respiration) during the actual time of recording.

When we consider the pressure-pulsation curve (Fig 1b) as a whole, we find that every single feature of our physical model appears confirmed. Apart from the actual drop at diastolic pressure, the record shows how, well above systolic pressure, the artery begins to be opened at the upper end of the constriction at the peak of each pulse-cycle (edge-effect). Here the pulsations are intermittent, and this is shown by the length of the horizontal portions of the record between the individual peaks. As the constraining pressure is lowered, the artery under the cuff remains closed for shorter and shorter periods, this being shown by the progressive decrease in the lengths of the horizontal portions of the record. Finally, there comes a point when the artery is open throughout the whole of each pulse-cycle and this, by definition, is diastolic pressure. The record shows that the disappearance of the horizontal portions coincides exactly with the fall in amplitude of the pulsations associated with diastolic pressure.

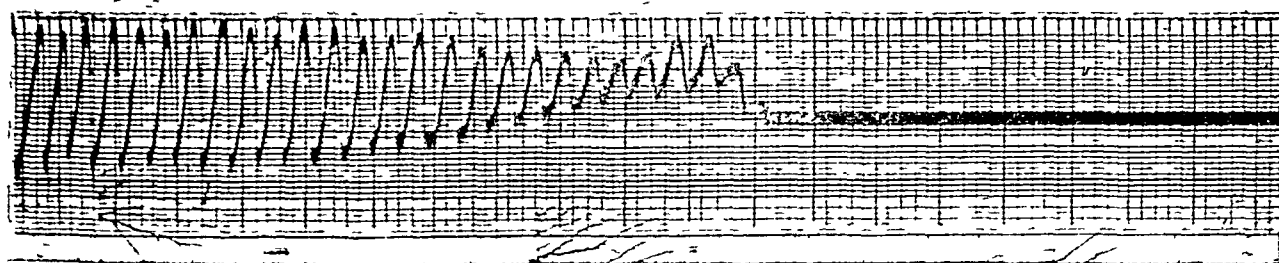
Theory and observation thus provide us with an independent confirmation of our criterion for diastolic pressure. When the observation is carried out visually by the anaesthetist, this change is clearly marked by an alteration in the character of the pulsations which, above diastolic, are jerky movements of the light-spot, and which change to unhindered smooth oscillations at the diastolic pressure. At the same time there is a marked shift in the zero position (for which there are theoretical reasons of a more complex nature) and these two additional features greatly facilitate the determination.

The records thus show that the simple physical model is confirmed by the observed behaviour of the artery to an astonishing degree, since it has to be remembered that the diastolic criterion was worked out theoretically even before the first recording-unit was built. The same is true for the systolic criterion. Claims have been made of observations of systolic pressure on the basis of a characteristic change in

the pulsations in a single cuff. This may, at first sight, seem reasonable for, when the constraining pressure is lowered below systolic pressure, blood will begin to flow underneath the cuff. However, it must be remembered that this change is bound to be a gradual one because of the limited size of the cuff. In fact, the pressure which it exerts on the limb is non uniform, and pressure pulsations will begin to be observed as soon as the pressure exerted anywhere on the limb-section falls below systolic.

This point is well illustrated by our record (Fig 1c), which shows no discontinuity at systolic pressure. As is to be expected, the rate of increase of the amplitude of pulsations is slightly accentuated in the neighbourhood of systolic pressure, but this is definitely an effect of the second order which is quite unsuitable as a criterion for determination. Even so, instruments attempting to make use of this as a criterion have been designed (cf Plesch, 1930). This is, of course, the reason for our use of two cuffs. Record 1c shows

FIG 6 INFLUENCE OF RESPIRATION ON SYSTOLIC RECORD



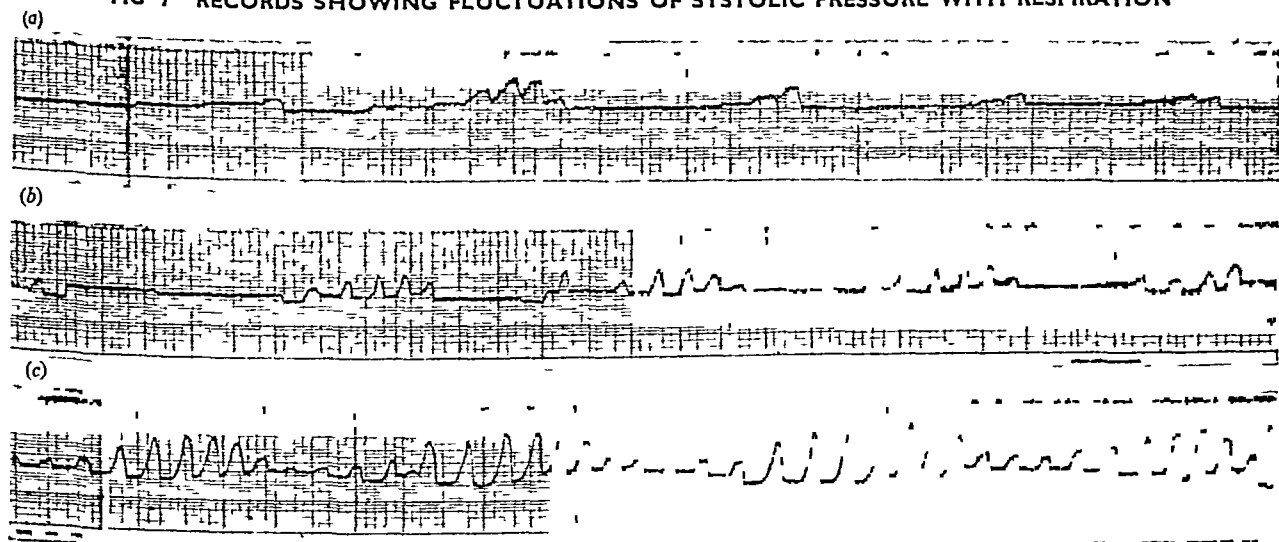
After the initial pulsations there is a slight decrease in amplitude [Read from right to left.]

The dominant feature of the situation is that the edge-pressure exerted is less than the central pressure, and this leads to the phenomenon of the edge-effect already described. As the cuff-pressure is lowered, the edge-effects penetrate further and further centrally, until, when the central pressure exerted by the cuff falls to systolic, the whole arterial section begins to open at each pressure-peak. This transition is gradual and, for practical purposes, there is no sharp criterion to indicate the point at which the edge-effects merge into a true pulsation of the whole section of artery beneath the cuff.

how unambiguous a criterion is obtained with our method, the result being found to be coincident with simultaneous auscultatory determinations.

Another interesting question is that of possible dynamical effects (Macintosh *et al.*, 1943), which have been completely neglected in our theory, the pressure pulsations being computed solely from the static volume-changes in the artery and cuff. Thus, when systolic pressure is being determined, the first blood passing beneath the constraining cuff will be expected to produce only a rise in the volume of the artery

FIG 7 RECORDS SHOWING FLUCTUATIONS OF SYSTOLIC PRESSURE WITH RESPIRATION



For all records the pressure in the recording cuff [B in Fig 2] was maintained at 80 mm Hg while that in the constraining cuff [A in Fig 2] had the constant values for the 3 different records of (a) 128 mm (b) 118 mm (c) 108 mm. The amplitude of pulsations varies with the respiratory cycle [Read from right to left.]

beneath the detecting cuff. Again the record (Fig 1c) provides a full confirmation of our theory. The first pressure-pulsations do not show a pressure-wave but a mere stepwise rise of the arterial volume, demonstrating that, as we anticipated, static volume-changes are the only ones producing first-order effects.

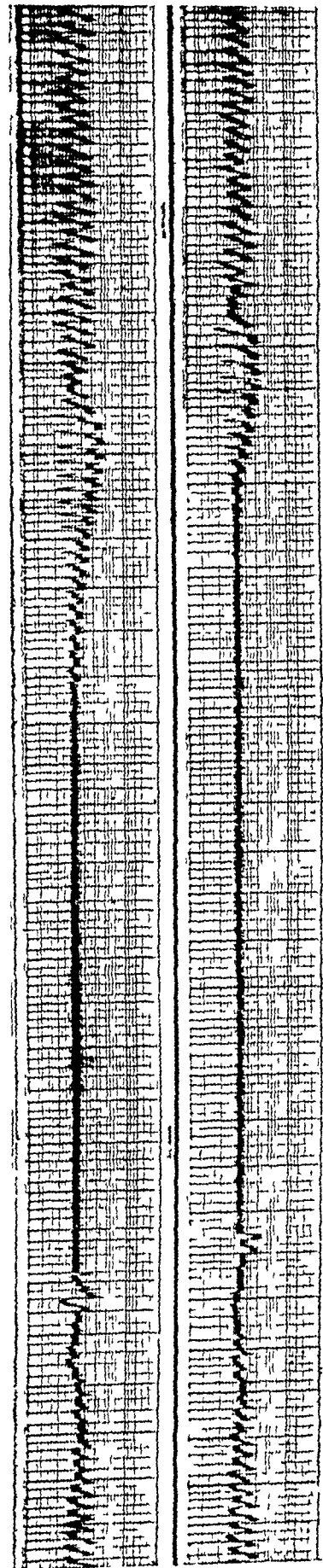
Natural and Induced Fluctuations

The determination of systolic pressure (Fig 1c) also serves to emphasize the occurrence of natural fluctuations of the characteristic pressures already mentioned in connection with the determination of diastolic pressures. The straight line in the record, above pressures of 130 mm, shows that in this pressure-range the artery is completely occluded throughout the pulse-cycle. However, if the value of systolic pressure varies with the respiratory cycle, the sharp onset of pulsations should occur at different pressures depending on the phase of the respiratory cycle. We have often observed that after pulsations have started they may decrease again, as in Fig 6. This is due to the fact that after the first pulsations were recorded the systolic pressure decreased.

The question arises as to whether this decrease is due to natural fluctuations in systolic pressure, or whether it is due to possible changes in the characteristic pressures caused by the measurement of blood-pressure itself. A decision in favour of the former alternative could be made by experiment. Fig 7 shows three pulsation-records in which the pressure in the recording cuff was kept at 80 mm, while that in the constraining cuff had the constant values (a) 128 mm, (b) 118 mm, (c) 108 mm. As will be seen, pulsations occur in all three records, but their size varies periodically, the period of variation being that of the respiratory cycle. In (a) and (b) the pulsations occur intermittently in groups separated by straight lines. In (c) the pulsations occur throughout, which means that there was no phase of the respiratory cycle in which systolic pressure fell below the cuff-pressure of 108 mm.

The experiment shows that in this case the systolic pressure certainly varied from values above 128 to values below 118, and that these variations are due to respiration, in this case rather deep. The variations between the individual pulse-waves in record (a) were artificially produced by varying the depth of the individual inspirations. Thus, in the present case (healthy male, aged 37) any determination of systolic pressure to more than 10 mm accuracy would be arbitrary. The effect varies very much between individuals and with the depth of respiration, but our records tend to show that reliance on "accurate" blood-pressure determinations, especially, for example, as a criterion of physical fitness, is open to criticism.

In the case of the anaesthetized patient, observation of these variations may yield additional information as to the state of the patient. This can easily be done with the sphygmoscope described above, the constraining cuff being set at pressures which, for example, just leave the maximum pulsation in each cycle, or which just leave all the pulsations throughout the cycle. In such cases it is clear that variations in blood-pressure will accompany the administration of anaesthesia both because of the effect of the anaesthetic on the vascular system, and because of its effect on the respiratory system. It is hoped that the instrument will help those anaesthetists who are interested in these problems.



The only feature of our observations which does not completely coincide with the mathematical theory is that of pressure-dependent coupling of cuff and tissue, an effect which was not foreseen, either by ourselves or by our critics. If this effect were not present, pulsations should still occur at zero cuff-pressure, and this is not the case. According to the theory there should be a linear dependence between the size of pulsations and the cuff-pressure below diastolic, and all our records show that, within the limits of accuracy, the actual relation is linear. This shows that, fortunately, the neglected coupling-effect must also depend linearly on the cuff-pressure. Changes in the size of pulsations observed at cuff-pressures below diastolic will therefore

FIG 8
EFFECT OF
INSPIRATORY
BREATH-HOLDING
ON
PULSE-PRESSURE

The record becomes practically horizontal, indicating that the subject's systolic pressure has fallen far below the cuff-pressure of 80 mm Hg. On release of the breath, there are changes during gasping, followed by resumption of normal rhythm.

[Read from right to left]

[left]

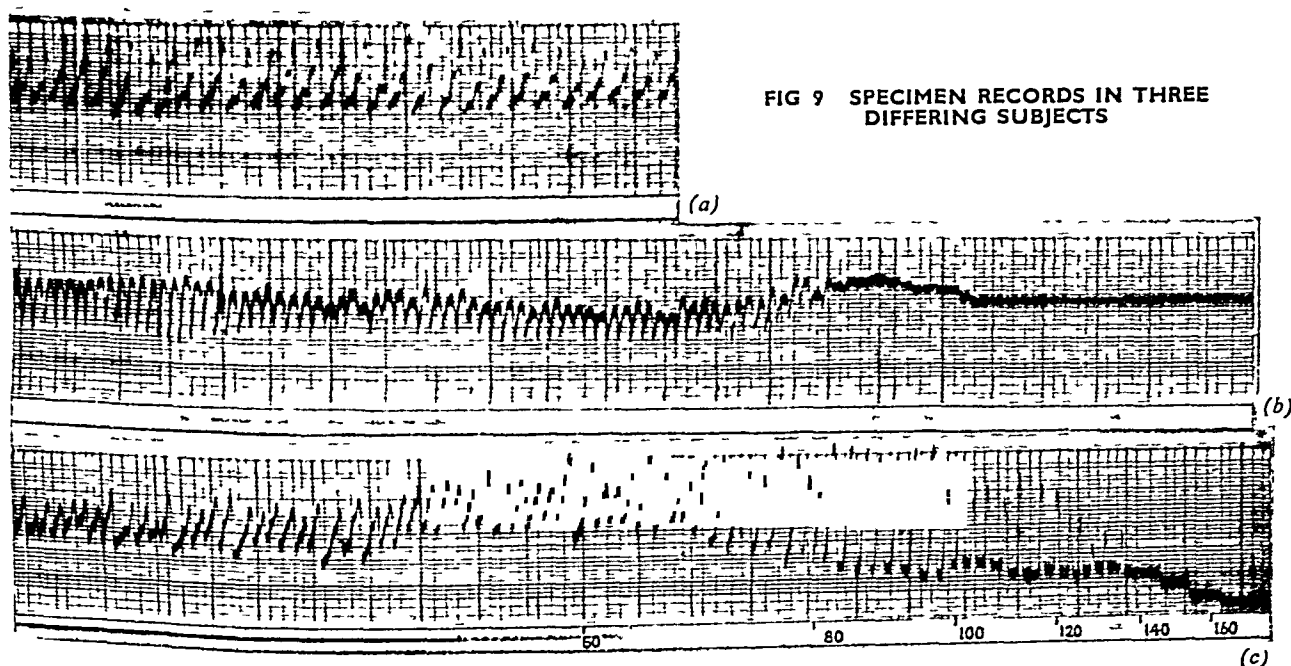
remain an indication of changes in pulse pressure as originally postulated

Examples of artificially produced changes in pulse-pressure are shown in Fig 8, which is a record taken on the arm with a cuff-pressure of 80 mm. First, the variation of pulse-pressure with respiration can be clearly seen. Then the subject (healthy male, aged 27), inhaled and began to hold his breath. After a time the record becomes practically horizontal, indicating that the subject had forced his systolic pressure below the cuff-pressure. On release of the breath, changes during gasping can be seen, and the normal rhythm then re-establishes itself. It is of interest to note that the lower record, which is a repetition of this experiment, is an almost exact duplicate of the first.

Other information of clinical value can be obtained from

Our own problem was somewhat different. The application of physics to clinical medical problems does not allow any simplification of the experimental conditions, such as is used by the physiologist. In consequence, therefore, any simplification must be introduced in the method adopted for investigation. The present account shows that this can be done with some degree of success, provided that a correct choice is made of the parameters sure to yield first-order effects. One cannot help feeling that in many cases where physical methods could be applied to medical problems, the real difficulty lies, not with the physical or mathematical methods, but in the recognition and selection of the important parameters.

ACKNOWLEDGMENTS—Our thanks are due to Dr F Barnett Mallinson for his constant help and advice in the development



a Pulse-curve of a healthy adult. b Systolic record of a healthy child aged 5 (irregularities due to muscular movements)
c Diastolic record of an adult with heart disease [Right to left.]

records of the pulse-curve. The three records, Fig 9, show (a) the pulse-curve of a normal adult, (b) the systolic record of a child, and (c) the diastolic record of a patient suffering from heart trouble.

Conclusion

The gratifying results of this discussion of the photographic records show that it is possible, within astonishingly wide limits, to make use of a simple physical model amenable to mathematical treatment, for the elucidation of somewhat complex clinical conditions. The medical man, and, to a certain extent, the physiologist, are accustomed to dealing with problems determined by so large a number of parameters as to make a simple analysis impossible. Nevertheless the physiologists have succeeded, by the use of the methods of physics, in deriving much information of a detailed nature

of the clinical model, to the Medical Research Council for a personal grant to one of us (K M.), and to Messrs J H Pye and E Root, of Clifton Instruments Ltd, Cambridge, for producing the sphygmoscope and sphygmograph in a form suitable for clinical use. Fig 1 & 2 are reproduced by kind permission of the editor of the *British Journal of Anaesthesia*.

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THE NATURE OF MENINGITIS FOLLOWING SPINAL ANAESTHESIA AND ITS PREVENTION

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Accidental infections produced by diagnostic or therapeutic proceedings are of much more frequent occurrence than the number of reported cases would suggest. There is a natural reluctance to publish anything which may appear discreditable, and unless investigation has revealed a previously unrecognized source of infection, there may be little object in doing so. It is therefore probable that meningitis following spinal anaesthesia has been far commoner than the literature of the subject would suggest. There are nevertheless fairly numerous records of it, some of which put forward an explanation on which subsequent findings have cast serious doubts.

So-called Aseptic or Chemical Meningitis

It has been assumed that the inflammatory changes produced in the spinal meninges are simply the result of chemical irritation by the anaesthetic. The principal paper in which this explanation is accepted is that of Livingstone, Wellman, Clark & Lambros (1943) who describe 2 personal cases and review those of six other authors; these comprise 8 cases with 3 deaths. It is a noteworthy fact that although the meningitis in some of these cases was frankly purulent—the cerebrospinal fluid cell-count in one of the patients studied by Livingstone and his colleagues was 9,600 per mm³—in no single instance was any micro-organism cultivated from the fluid. Details of the aseptic technique employed are not described; it is therefore not possible to decide whether bacterial contamination could have occurred in ways to be considered later. A single similar occurrence is described by Nunziata, Castelluccio & Peralta (1944), a purulent meningitis followed spinal anaesthesia, and although no micro-organism could be found in the cerebrospinal fluid, the treatment adopted was the intrathecal injection of soluble sulphapyridine. A paraplegia resulted and the patient died. This complication was, of course, a true example of chemical damage to the cord.

The supposition that spinal anaesthetics in concentrations used clinically will produce acute inflammatory changes in the meninges is unsupported by experimental evidence. This hypothesis also fails to account for variation of their effect in different individuals; why should only a very small proportion of patients react in this way to the same stimulus?

The Sheffield Series. Incrimination of "Sterile" Water

It was reported by Barrie (1941) that during a certain period at the Royal Hospital, Sheffield, 11 out of 96 patients who were given a spinal anaesthetic in one operating-theatre developed a meningitis subsequently. The cell-count in the cerebrospinal fluid varied from 9 to 1,100 per mm³, no

bacteria were found in these fluids, except that a culture from one of them contained 3 colonies of a Gram-negative bacillus, which at the time was disregarded. One of these cases was fatal. The lumbar-puncture needles used were sterilized in formaldehyde vapour, and rinsed before use in water supposed to have been sterilized by filtration. This came from a Berkefeld filter fed directly from the roof-tank, and a non-saccharolytic Gram-negative bacillus similar to that cultivated from one of the cerebrospinal fluids was cultivated from not only the inflow but the outflow of this filter. When the use of this water was stopped, no further cases of meningitis occurred.

A further investigation at Sheffield prompted by this incident was undertaken by Smith & Smith (1941). By cultivating a large inoculum (4 to 15 drops) of cerebrospinal fluid in peptone-water at room-temperature, they showed that 89 (40%) of 223 specimens of cerebrospinal fluid contained living bacteria. These specimens were almost all from patients not suffering from meningitis, and should have been sterile. Cultivation of 154 of these specimens by usual methods at 37° C revealed contamination in only 15 (9.7%). Most of the positive cultures contained Gram-negative bacilli, some being *Ps. fluorescens* and others unidentified.

The meaning of these observations is that, for lumbar puncture by the methods then employed, apparatus was being used which was contaminated, probably by non-sterile water. The organisms found were mainly common water-bacteria, non-pathogenic in the ordinary sense, whose optimum-growth temperature is below that of the body; hence cultivation at a lower temperature more frequently reveals their presence. This conclusion was supported by two further observations: of 10 specimens of cerebrospinal fluid collected with adequate aseptic precautions, using needles sterilized by heat, only 1 yielded growth in culture (a diphtheroid bacillus doubtless from the skin). Secondly, "sterile" water from 4 different hospitals was found frequently to contain living bacteria, especially if the bottle had been in use before being sampled.

The contamination of syringes and other instruments with nondescript Gram-negative bacilli by rinsing them in water of this kind must have been observed by many, although its particular danger in connection with spinal anaesthesia and lumbar puncture generally was fully recognized only after the publication of the Sheffield study.

I recollect an occasion some twenty years ago when three patients in one ward were reported to be suffering from septicaemia due to "*B. faecalis alkaligenes*", this name had been given to the organisms cultivated from the blood for the inadequate reason that they were motile Gram-negative bacilli not fermenting any sugars. The syringes used for all these blood-cultures proved to have been taken from an antiseptic solution and rinsed in distilled water which was not even alleged to be sterile. The same organism was readily cultivated from this water. More recently I have examined specimens of cerebrospinal fluid from a number of cases of meningitis following lumbar puncture, and have cultivated unidentified Gram-negative bacilli from several of them. Rinsing in supposedly-sterile distilled water of the needle used, or of the manometer attached to it, was regarded as the source of contamination in these cases. In the hospital in which I was then working, and in which these cases occurred, 30 out of 42 specimens of cerebrospinal fluid collected at this time gave growth when 0.5 cm³ of fluid was

cultivated in peptone-water at room-temperature—a higher proportion than in the specimens examined by Smith & Smith

Meningitis due to Water Bacteria Nature and Diagnosis

These water-bacteria are entirely non-pathogenic in the ordinary sense, and some of them appear to be incapable of growth, at least under some *in vitro* conditions, at body-temperature, how, then, is it possible that they should cause a severe and even fatal purulent meningitis? This question cannot be answered fully without further study, but the following facts may have a bearing on it

In the first place, every experimentalist knows that the intrathecal route of inoculation is the most sensitive test of pathogenicity, and clinical experience shows abundantly that accidental infection has graver consequences in the central nervous system than in any other part of the body. It may logically be concluded that bacterial contamination which would readily be overcome in other organs or tissues can have a devastating effect in this situation

Secondly—although this is in part conjecture—cerebrospinal fluid is likely to be an admirable medium for the growth of bacteria accustomed to a fluid habitat containing a low concentration of nutrients. Such an organism introduced into the spinal canal might multiply extensively within a few hours, its active motility aiding widespread dissemination. If sufficient numbers are introduced, as may occur when any fluid is injected into the spinal canal, it is possible that their presence might excite an inflammatory reaction without further multiplication. Assuming that reported cases of aseptic meningitis have been of this nature, there are thus three possible explanations for the sterility of the cultures made: (i) that the organisms are incapable of growth under any conditions at 37° C and have not, in fact, multiplied in the spinal canal at all, (ii) that they have multiplied but have been destroyed by phagocytosis, (iii) that they are capable of growth in cerebrospinal fluid at body-temperature, but not, at that temperature, in the culture-medium used

Only further study of the combined nutritional and temperature requirements of strains of Gram-negative bacilli isolated from cases of this type of meningitis can finally elucidate this question. That some of them will grow in ordinary culture at 37° C is shown by one of Barrie's cases and several in my own experience

The examination of cerebrospinal fluid from cases of meningitis suspected to be of this nature should include study of films of the deposit stained with Sandiford's (1938) stain¹. Gram negative organisms are thus much more readily distinguished than in preparations in which they are of the same colour as the background. Cultures should be made not only on blood-agar, incubated at 37° C, but on plain agar and in peptone-water, to be incubated at 25° C or merely kept at room-temperature

Other Sources of Contamination

As has recently been pointed out by Evans (1946), there are several possible sources of contamination when meningitis follows the administration of a spinal anaesthetic. They include the anaesthetic solution itself (although this has never been directly incriminated), the instruments used,

the hands of the operator, and the skin of the patient. Evans (1945) himself has reported 2 fatal cases of meningitis due to *Ps. pyocyanea* following spinal anaesthesia in which the source was not traced. The syringe and needle used had been kept in spirit and were rinsed in sterile saline. This saline was believed to be above reproach, but "*Ps. pyocyanea* had recently been much in evidence in the hospital" and had been found in a specimen of cerebrospinal fluid from a patient without meningitis, this contamination being traced to "sterile" distilled water kept in a Winchester-quart bottle².

Contamination from the skin, whether of patient or operator, is a likely cause of staphylococcal meningitis, such a case is reported by Worth (1945), in which the primary lesion was an interspinous abscess following diagnostic lumbar puncture. Another possible source of contamination was reported by Hewer & Garrod (1942), ampoules of spinal anaesthetic solution which formerly had their description etched on the glass were supplied during the war with paper labels. These ampoules had been immersed in spirit to sterilize their outer surface and subsequently placed in sterile water in which the label came off. Bacteriological study showed that immersion in spirit does not sterilize a gummed label, the water in which this was soaked off consequently became heavily contaminated. Alternative methods suggested to avoid this risk were sterilization by formaldehyde vapour, or the omission of any attempt to sterilize the whole outer surface, the ampoule being held in a sterile towel and the neck etherized before opening.

Recommended Aseptic Technique

The induction of spinal anaesthesia is an operation which calls for full aseptic technique. The operator should wear gloves, gown and mask, and particular care should be given to the disinfection of the patient's skin. Evans (1946), who fully describes these and other precautions, recommends that the needle and syringe used should be boiled. In this connection reference should be made to the recent Medical Research Council (1945) memorandum on the sterilization of syringes³. From experiments described here it is clear that no chemical method of sterilizing syringes is satisfactory. Spirit, in particular, fails to disinfect the crevices in the interior of a syringe, especially of the Record (glass and metal) type.

In view of these findings it would be rash to trust disinfection in spirit for lumbar-puncture needles. Disinfection by heat of all apparatus used in connection with lumbar puncture for any purpose is therefore strongly advisable. Boiling is a reasonably safe method but, as is pointed out in the memorandum, the ideal method is enclosure in a tube and sterilization by dry heat at 160° C for 1 hour. The only disadvantage of this method is that the cement of some metal-and-glass syringes melts below this temperature, all-glass syringes are therefore necessary. If these are used, the syringe, needle, and the manometer used in diagnostic lumbar puncture, can be encased and sterilized by dry heat, and thus kept ready for use at any time. This is the ideal method of sterilization, and should be much more widely used for this and a number of other purposes. It has the incidental advantage in connection with diagnostic lumbar puncture that the fluid is obtained in the pure state,

¹ [Sandiford's counter stain is made up as follows: malachite green 0.05 g, pyronine 0.15 g, distilled water to 100 ml. Apply for 2 minutes, flood off with water (but do not wash) and blot. Cells and nuclei stain bluish green. Gram-positive organisms are purple-black. Gram-negative organisms red. The stain keeps for about a month.—Ed.]

² [A Winchester quart is approximately 2.25 l.—Ed.]

³ [See B.M.B. 77/158 for a review of this memorandum.—Ed.]

unmixed with anything else Apparatus wet with water or saline may completely falsify the results of chloride estimation

The practice of placing sterile instruments ready for use in bowls of water, or of using such water to wash them free of a disinfectant, has been shown to involve serious risks Water or saline can be depended on to be sterile only if it has been autoclaved in a closed vessel with a protected rim, which is opened immediately before use After one such use the remainder should be discarded The quite prevalent idea that water is necessarily sterile because it has been distilled is entirely untrue, tap-water, filtered water, and any water, even previously sterile, which has been exposed to contamination, are all unsuitable as agents in an aseptic technique The existence of bacteria which can survive, and apparently even multiply, in such fluids deserves much wider recognition The elimination of such water from surgical use of other kinds would be a step in the right direction.

It seems at least probable, although admittedly it cannot

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be proved, that contamination with water-bacteria has been the cause of most cases of "aseptic" meningitis following spinal anaesthesia In the absence of any other reasonable explanation, this hypothesis deserves at least the fullest investigation in connection with any cases which may occur hereafter

Summary

1 There is good evidence for believing that many cases of "aseptic" meningitis following spinal anaesthesia are due to infection of the spinal canal by Gram-negative bacilli of types found in water used for rinsing syringes and needles The presence of such bacteria is not necessarily detected by ordinary methods of cerebrospinal-fluid examination

2 All apparatus used for lumbar puncture for any purpose should be sterilized by heat, preferably dry heat

3 Water used for surgical purposes and believed to be sterile is frequently not so The use of such fluids, unless from a freshly-opened vessel which has been autoclaved, is to be condemned

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TRICHLORETHYLENE AS AN ANAESTHETIC AGENT

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Historical

Trichlorethylene was introduced as a general anaesthetic in a somewhat unusual manner In 1939, the secretary of the joint Anaesthetics Committee of the Medical Research Council and the Royal Society of Medicine was approached by a chemist, Mr Chalmers, of Muswell Hill, who stated that trichlorethylene appeared to be an excellent general anaesthetic and suggested that it might be used by anaesthetists This he did as the result of experiments with the drug which he had made upon himself

On looking into the matter, the Committee found that the only published work on the use of trichlorethylene in human anaesthesia was a paper by Stricker, Goldblatt, Warm & Jackson (1935) in America, describing a series of 300 short administrations for minor operations The results were inconclusive as in the following year (1936) the Council on Pharmacy and Chemistry of the American Medical Association considered that "the case had not been completely made out" for the usefulness of the drug

In these circumstances, it was considered worth while to investigate the effects of trichlorethylene fully with a view to finding out whether it had any place in anaesthesia, and the writer was asked to carry out this work The investigation was

done in the department of anaesthesia of St Bartholomew's Hospital, and the results were embodied in three papers (Hewer, 1941, 1942, 1943)

Since then the use of the drug has spread rapidly, and it is now generally recognized to have a definite place in anaesthesia in spite of certain disadvantages which will be referred to later

Chemical and Physical Properties

Trichlorethylene has the chemical formula CCl_2CHCl and is a colourless liquid with a specific gravity of 1.47, a vapour density of 4.53, and a boiling point of 87°C It is not inflammable, and its vapour will not explode when mixed in any proportion with air

The liquid has an odour resembling that of chloroform but without its pungency It is practically insoluble in water, but will mix with any proportion of ether Commercial trichlorethylene is used for such purposes as the dry-cleaning of clothes and the degreasing of metals, but this grade must not be used for anaesthesia as various impurities can give rise to toxic symptoms such as vomiting, vertigo, optic neuritis, and nerve palsies A specially purified preparation known as "Trilene" has been marketed in Great Britain for inhalation anaesthesia This is stabilized by the addition of 0.01% thymol and coloured blue for easy identification

Effects of Inhalation of Trichlorethylene

The first stage of anaesthesia is characterized by a marked degree of analgesia which renders the drug very useful for much minor surgery, painful dressings, dental drilling and other procedures where surgical anaesthesia is unnecessary or undesirable Trichlorethylene analgesia is also tending to replace nitrous-oxide-and-air in midwifery in many parts of Britain

The first plane of the third stage of anaesthesia is marked by shallow¹ slow respiration with the patient a normal colour, and with blood-pressure and pulse-rate within the usual limits. Muscular relaxation is variable, but if it is insufficient for the operation in hand, no attempt should be made to deepen anaesthesia with trichlorethylene but a change to ether should be made temporarily, or, alternatively, relaxation can be obtained by other means, such as nerve-blocking or the intravenous injection of pentothal sodium or curare².

If the narcosis is pushed to the deeper planes of the third stage, the respiration-rate will rise, the tidal exchange will fall, and the patient's condition will rapidly deteriorate. Tachypnoea should always be regarded as a sign of over-dosage with trichlorethylene.

Irregularities of the pulse are common as with all inhalation anaesthetics. Recent work with the electrocardiograph (Barnes & Ives, 1944) shows a great variety of changes from the normal rhythm. It seems probable that most of these are of little clinical importance, except possibly multifocal ventricular tachycardia which, in the case of chloroform, can precede ventricular fibrillation. This type of arrhythmia has been recorded in about 10% of cases anaesthetized either with trichlorethylene or with cyclopropane, but primary cardiac failure is fortunately extremely rare with either of these drugs.

Methods of Administration

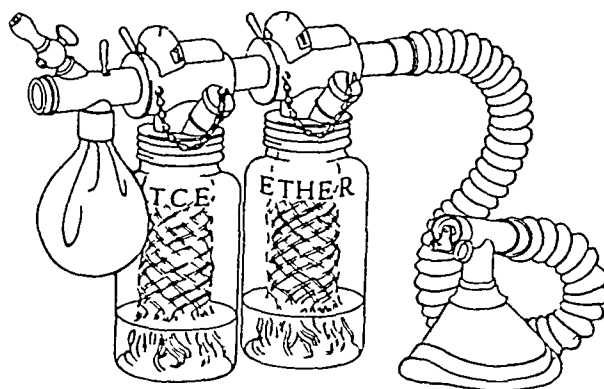
Since trichlorethylene has a relatively low volatility, the open-mask method of administration is unsatisfactory, as the gauze would soon become saturated.

FIG 1 TRICHLORETHYLENE AUTO-ANALGESIA



Hill's apparatus for self-administered trichlorethylene. The apparatus is shown in the position used for dental analgesia.

FIG 2. INHALER FOR FULL ANAESTHESIA WITH TRICHLORETHYLENE



'Draw-over' inhaler for use with trichlorethylene (TCE) when full surgical anaesthesia is required. If necessary ether may be added by adjusting the tap of the second bottle.

If general analgesia only is required, self-administration can be taught to a patient quite easily, using a simple "draw-over" apparatus such as Freedman's. An air-hole closed by the patient's finger is used, as in Minnitt's gas-air analgesia apparatus. This apparatus has proved very satisfactory in midwifery.

For analgesia during dentistry (e.g. painful drilling) a blow-through apparatus such as that of Hill (1944) is more reliable, owing to the difficulty of obtaining a perfectly airtight fit for the nose-piece. The patient squeezes a rubber hand-bulb which supplies a weak vapour to the nose as required (Fig 1).

In order to secure full anaesthesia with trichlorethylene and air, an inhaler such as Marrett's is quite satisfactory. The vapour concentration is adjustable, and a second bottle enables deep narcosis to be secured with ether if necessary (Fig 2).

Should a gas-and-oxygen apparatus be available, trichlorethylene can be placed in the chloroform bottle and used as an adjunct to nitrous-oxide-and-oxygen. The amount necessary is extremely small, averaging only a few minims³ per hour. When narcosis has been in progress for some time, the trichlorethylene can often be turned off altogether for considerable periods. This form of anaesthesia is most useful for the many operations in which complete muscular relaxation is unnecessary but no attempt should be made to "push" trichlorethylene or tachypnoea and other signs of overdosage will appear.

The total rebreathing technique with CO₂ absorption by soda-lime is not suitable for use with trichlorethylene as in certain circumstances a chemical reaction can occur which may cause the formation of toxic products (Carden, 1944).

After-effects

Post-anaesthetic nausea and vomiting are definitely less than after ether narcosis, and patients who have experienced each usually volunteer the statement that they prefer trichlorethylene.

¹ [See B.M.B. 817 a report of an experimental investigation on the cause of this shallowness of respiration.—Ed.]

² [See B.M.B. 824.—Ed.]

³ 1 minim = 0.06 ml.

Pulmonary complications can occur after any operation performed under any type of anaesthesia or analgesia, and their etiology is far from simple. It would appear, however, that dilute trichlorethylene vapour causes practically no irritation to the respiratory passages and does not stimulate the production of saliva and mucus to anything like the same degree as ether.

Up to date, only one case of liver-damage has been reported from the use of trichlorethylene.

ACKNOWLEDGMENT—Fig. 1 is reproduced from Hill (1944) by permission of Dr Basil Hill, Fig. 2 is reproduced from Hewer (1942).

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Conclusions

From the foregoing remarks it will be seen that purified trichlorethylene has been shown to be an excellent inhalant drug for producing general analgesia. It is also useful for light general anaesthesia, preferably given with nitrous-oxide-and-oxygen, especially if an ignition risk is present. Trichlorethylene should not be used to produce profound narcosis and should not be given in a closed-circuit apparatus with soda-lime.

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CURARE

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Historical

In the sixteenth century, explorers of South America, such as Magellan, discovered that some of the natives of the Orinoco region were preparing a decoction from certain plants and were smearing it on the arrow-heads which they used for shooting big game. An animal hit by such a poisoned arrow usually became paralyzed almost immediately.

In 1800, von Humboldt found that the arrow poison was made from a particular type of creeper which was named later *Strychnos toxifera*.

Some sixty years later, Claude Bernard (1865) and others showed that the active principles of the poison were contained in a group of alkaloids which were collectively called "curare".

Research into the exact effects of curare on the human body was held up for a long time owing to various toxic effects, such as bronchospasm, which are now known to be due to other substances in the crude curare. Even so, some success was obtained (Cole, 1934) in treating tetanic spasms by this agent.

In 1935, H. King, of the National Institute for Medical Research, London, succeeded in isolating the pure alkaloid which was called *d*-tubocurarine chloride. From this moment, knowledge of the action of the drug increased rapidly and it quickly came into use as a therapeutic agent.

It was soon found that pure curare could be used to minimize the risk of trauma during electro-convulsive therapy in mental patients. If the drug is injected intravenously just before the current is switched on, the resulting convulsion is greatly "softened" and fractures and dislocations are much less likely to occur.

In Canada, intravenous curare was first employed as a muscle relaxant during light anaesthesia by Griffith &

Johnson (1944), and this proved so successful that its use has spread rapidly.

Action

It is probable that the main action of pure curare is to neutralize the acetylcholine mechanism of transmission of nerve impulses at the myoneural junction. Thus the voluntary muscles are paralyzed, the diaphragm being affected last.

For all practical purposes, the effect of injecting curare can be regarded as giving the patient a transient attack of myasthenia gravis and the existence of this disease appears to be the chief absolute contra-indication to the method.

The antidote for overdosage is the same as the drug used in the treatment of myasthenia gravis, viz. prostigmine.

Curare causes temporary loss of tone and peristaltic activity of the smooth muscle of the intestine (Gross & Cullen, 1945), but has little effect on the stomach.

In normal dosage, curare has practically no effect on the central nervous system, so that it is neither an anaesthetic nor an analgesic. When injected intravenously into a lightly anaesthetized patient, complete muscular relaxation occurs within a minute or so with no appreciable fall in blood-pressure. This has hitherto proved impossible by any other means and must be regarded as a great advance in anaesthesia. It would seem that curare provides all the advantages of a high spinal block (relaxed, silent abdomen, etc.), without the disadvantages and dangers (fall of blood-pressure, contracted intestines, sequelae, etc.). It is a curious fact that visceral traction, etc., in a curarized patient does not produce the falls in blood-pressure that one would expect in a lightly narcotized subject unprotected by splanchnic block. It would appear that some of our current views on the production of traumatic shock may have to be modified as the result of this observation.

Bronchospasm is rare, but has been reported, while gross overdosage will produce diaphragmatic paralysis. If this occurs, gaseous exchange must be maintained by means of controlled respiration until natural breathing is resumed.

Elimination of curare takes place fairly quickly, partly by destruction in the liver and partly by being excreted unchanged by the kidneys.

Preparations and Dosage

At the present time there are two preparations of purified curare on the market and unfortunately they differ in potency.

"Intocostin" (Squibb) is put up in bottles of 5 cm³ and 10 cm³ and consists of a sterile solution of 20 mg of "curare extract" per cm³ with 0.5% chlorbutanol added as a preservative. The initial intravenous dose to a lightly anaesthetized adult is from 2.5–3 cm³ of Intocostin. This is normally given before the peritoneum is opened and may suffice for the entire operation. For long procedures, however, such as gastrectomy, an additional 1.5–2 cm³ may have to be given just prior to closing the abdomen if muscular relaxation has become inadequate. Intocostin is a purified extract from the plant *Chondodendron tomentosum*.

The second preparation is known as "curarine chloride" (Burroughs Wellcome) and is put up in 100 mg glass ampoules as a powder. This product is claimed to be identical with the *d*-tubocurarine chloride originally isolated by King. It is considerably more potent than Intocostin and 25–30 mg is usually an ample total dose.

The anaesthetics committee of the Medical Research Council and the Royal Society of Medicine are endeavouring to bring about standardization in potency of all curare preparations, but in the meantime it is essential to realize the difference which at present exists.

Administration

Up to now, the main indication for the administration of curare in surgery has been for major abdominal operations in "difficult" subjects. Many muscular or short-necked, plethoric and emphysematous patients cannot be maintained in a state of complete muscular relaxation without large doses of general anaesthetics or the addition of various types of nerve- or field-blocking or spinal analgesia. All these methods have their disadvantages whereas a single intravenous injection of curare will produce complete relaxation within two minutes in the most recalcitrant subject, without unpleasant side actions.

The actual technique used by the writer is to induce anaesthesia by an ordinary method such as pentothal sodium, followed either by cyclopropane or by nitrous oxide-oxygen.

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with minimal trichlorethylene. Nasal intubation is then performed and, when endotracheal anaesthesia is progressing smoothly, the patient is transferred to the operating table with the arms outstretched upon a double arm splint. In right-handed patients, an intravenous drip-saline is set up for the left arm while the blood-pressure cuff and stethoscope are attached to the right one. By this time the surgeon should be ready to open the peritoneal cavity and since the general narcosis is being maintained at the lightest possible level, it is almost certain that the muscles of the abdomen will be rigid. The initial dose of curare, as discussed above, is now injected from a syringe into the tubing of the intravenous drip as near to the needle as possible, the tube being pinched proximally during the actual injection. Within two minutes a dramatic change should have occurred, the abdominal wall becoming as slack and flaccid as during a high spinal block. This state should persist for the intra-abdominal part of the operation, a second smaller dose being sometimes needed for closure. The general anaesthetic should not, as a rule, be ether, as this in itself has a curariform action so that less of the drug can be used and the results are not so good. An extremely light plane of narcosis can be maintained, but care must be taken that the patient does not actually become conscious or he may feel pain. Endotracheal anaesthesia is recommended as, if bronchospasm should occur or diaphragmatic paralysis result from overdosage, the situation is readily controlled. Although prostigmine is the physiological antidote to curare, it should be rarely necessary, as the respiratory exchange can be maintained easily with any modern gas-oxygen apparatus should apnoea occur temporarily.

Sequelae are conspicuous by their absence and the only after-effects attributable to curare which have occurred in the writer's practice are occasional complaints of difficulty in opening the eyes, which may persist for a few days. This is, of course, also a symptom of myasthenia gravis.

In conclusion, it would appear that curare is likely to prove a notable advance for achieving perfect muscular relaxation during light anaesthesia.

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CONTROLLED - RESPIRATION ANAESTHESIA

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Controlled respiration "involves the consideration of apnoea and artificial respiration by rhythmic pressure on the breathing bag. Actually it means that the anaesthetist deliberately takes the function of pulmonary respiration from the patient into his own hands" (Guedel, 1940). In accordance with the fundamental concepts of the physiology of respiration, apnoea during anaesthesia will occur when the carbon-dioxide tension in the blood is insufficient to stimulate the

respiratory centre. This results when the carbon dioxide tension is lowered by artificial hyperventilation, or when the respiratory centre is sufficiently depressed by narcotics or anaesthetic drugs, e.g. opiates, short-acting barbiturates, cyclopropane, or by a combination of these causes. Controlled respiration, which implies the occurrence of apnoea in accordance with these principles, has been developed in recent years mainly as a solution to two problems in inhalation anaesthesia: the production of relaxation with cyclopropane, and the control of the respiratory disabilities which complicate thoracic surgery.

Applications

Cyclopropane is a potent respiratory depressant, and it is unusual to obtain sufficient relaxation for abdominal operations with this anaesthetic before respiratory arrest occurs. But an increased depth of anaesthesia beyond this point, i.e. greater muscular relaxation, will accompany increasing

cyclopropane tension in the blood. This can be brought about by rhythmic compression (about 18 per minute) of the reservoir bag in order to maintain the natural functions of respiration, the intake of oxygen and output of carbon dioxide, and at the same time to present an atmosphere containing sufficient cyclopropane to produce the desired level of anaesthesia. In this manner the sphere of usefulness of this agent, and its attendant advantages, can be extended to the majority of abdominal operations. Controlled respiration is thus the means of utilizing the otherwise inaccessible "plane" of cyclopropane anaesthesia of which the upper level is respiratory arrest, and the lower level commencing circulatory depression.

In abdominal work, relaxation is all-important. For intrathoracic surgery relaxation is unnecessary, but the anaesthetist must be prepared to contend with paradoxical respiration and other mechanical respiratory difficulties caused by an open pneumothorax. In most cases he must also offer a technique which permits repeated bronchial suction. Controlled respiration, *i.e.* intermittent positive pressure, provides a simple and completely effective method of overcoming the respiratory disabilities which an opening in the chest wall creates. Efficient respiratory exchange can be maintained under all circumstances, including the simultaneous opening of both pleural cavities. In addition, the non-irritating nature, rapidity of action and elimination, and low general toxicity of cyclopropane make this agent of particular value in thoracic surgery.

However, one technical point is noteworthy if this method is used for intrathoracic procedures other than total pneumonectomy. Care must be taken by suitably adjusted pressures and frequent observations, to prevent the complete collapse of the healthy lobes (should these be non-adherent) on the operated side. Complete collapse, particularly over a long period, favours the undesirable complication of failure to re-expand during the immediate post-operative period (Maier, 1944).

The use of *continuous* positive pressure during intrathoracic operations is an alternative procedure. The relative merits of these two techniques have been thoroughly discussed in recent papers (Beecher, 1940, Bradshaw, 1939, Crafoord, 1940, Neff, Phillips & Gunn, 1942, Nosworthy, 1941).

Both in upper abdominal and in thoracic surgery, controlled respiration offers one direct advantage, for what it is worth, that the operative field can be rendered motionless if desired by momentary discontinuation of breathing-bag movements.

Technique of Controlled-respiration Anaesthesia with Cyclopropane

Omnopon $\frac{1}{2}$ grain [20 mg] and scopolamine $\frac{1}{150}$ grain [0.5 mg] form suitable premedication for most adult cases before cyclopropane anaesthesia. Induction with a short-acting barbiturate (e.g. pentothal 0.5 g) is pleasant for the patient and has the additional advantage of affording a high degree of protection against cardiac arrhythmias during the ensuing anaesthesia (Guedel, 1940, Thienes, Greeley & Guedel, 1941). The accompanying respiratory depression is no disadvantage if controlled respiration is to be deliberately undertaken. A closed circuit with carbon-dioxide-absorption apparatus is naturally essential, either of

the types in common use at the present time, *i.e.* to-and-fro or circuit principles, being satisfactory.

A suitable procedure for the introduction of cyclopropane after pentothal is to start with a litre of air in the reservoir bag and with the absorber out (to hasten induction), and then to start with a flow of cyclopropane and oxygen at a rate of 500 cm³ of each per minute, assisting inspiration by pressure on the bag if necessary. After a few minutes the absorber can be connected, and controlled respiration can be started as spontaneous movements become inadequate. Cyclopropane flow can be reduced to an intermittent trickle, and oxygen to the basal rate of about 250 cm³ per minute, when the required depth is obtained. A detailed description of this form of technique has been given by Nosworthy (1941).

Once controlled respiration has been undertaken it is imperative to procure a completely airtight system. Apart from the waste of valuable gas, undesirable fluctuations in depth of anaesthesia will follow the repeated additions made necessary by a leaking apparatus or an imperfect fit between mask and face.

The occurrence during apnoea of laryngeal spasm as a vagal-traction reflex-effect is a very real problem in this type of anaesthesia. Interference with controlled respiration in this way, which is readily distinguishable from the resistance caused by the muscles of expiration, must for obvious reasons be avoided, either by the intelligent anticipation of surgical manoeuvres or by the use of an endotracheal tube. A tube should always be used if such reflexes are considered to be unpredictable. Some form of endotracheal technique is also obviously necessary if bronchial suction is to be performed. In any case a pharyngeal airway can be used with advantage from the outset.

The untoward effects of excessive endotracheal pressure have been made clear by Adams (1940), Macklin (1939), Marcotte, Phillips, Adams & Livingstone (1940). However, intermittent positive pressure up to as little as 10 cm water (which is undoubtedly safe) will be found sufficient for procuring effective ventilation with an open larynx under cyclopropane anaesthesia. A satisfactory procedure is to imitate the movements of normal sleep. Hyperventilation with its attendant alkalosis serves no useful purpose with this agent, and is to be avoided.

Estimation of Depth of Anaesthesia

Difficulties may be encountered when estimating depth of cyclopropane anaesthesia. These have been discussed by Gould (1941). In addition, the deliberate production of respiratory failure removes the greatest safeguard against overdosage (Beecher, 1940). From the moment apnoea occurs, respiratory movements are no longer available as a sign, and since the estimation of subsequent depth is clearly of paramount importance attention must be paid to every point which may provide relevant information. For example, the patient's respiratory behaviour following premedication and the induction-dose of barbiturate should be noted. Watch must be kept on the amount of anaesthetic added since the onset of apnoea. For this purpose accurate flowmeters are essential, though an estimate of the anaesthetic concentration actually being inhaled at any time can always be obtained by smelling samples of the mixture. Some part of the closed-circuit system of the apparatus can with advantage be provided with a sampling tube for this purpose.

When respiratory depression is only just sufficient to maintain apnoea, the slight rise in carbon-dioxide tension of the blood occasioned by short-circuiting the absorber for a few minutes will restart respiration. In these circumstances, the time required for spontaneous movements to return gives a measure of anaesthetic depth in terms of respiratory depression. But as a means of gauging deeper anaesthesia, when only a high carbon-dioxide tension will stimulate the respiratory centre, this latter method becomes impractical and theoretically undesirable.

The patient's own reflex activity is a guide to depth, e.g. responses evoked by manipulation of a bronchus during thoracic surgery. If due regard be paid to the nature of the surgical stimulation in progress at the time, the force required adequately to inflate the lungs during controlled respiration may also be used as a measure of depth (Morton, 1945). With increasing muscular relaxation and decreasing reflex irritability, progressively less resistance is offered to inflation.

Much useful information with respect to abdominal relaxation is also gained by noting not only the resistance offered to inflation, but also the relative extent of the resulting abdominal and thoracic movements. This latter point is often particularly well demonstrated in cases of perforated peptic ulcer. In these cases considerable rigidity usually persists under light anaesthesia, and the expiratory muscles offer resistance to inflation of the lungs. The inspiratory movements produced by bag pressures may be mainly thoracic. But as anaesthesia deepens and relaxation develops, inflation becomes easier and increasing diaphragmatic descent is evident from the increasing rise of the abdominal wall. When immediate and well-marked abdominal movement accompanies inflation with an endotracheal pressure of less than 10 cm. water, adequate relaxation for upper abdominal surgery is assured.

Strict attention must be paid to the effects of operative shock. In this connection shock and haemorrhage produce effects comparable with those of deepening the anaesthesia. Relative overdosage may easily occur, and the return of spontaneous respiration be undesirably delayed unless the anaesthetic-concentration is reduced. The rapidity of elimination of cyclopropane is one of the major advantages of this agent under these circumstances.

Return of Spontaneous Respiration

Due regard to the signs of depth enables the level of anaesthesia to be assessed relative to the threshold at which spontaneous respiration will return. Cyclopropane in a concentration in the neighbourhood of 75% "will produce apnoea with a threshold out of reach of any known stimulus" (Guedel, 1940). At the lower concentrations more usually employed, respiration can be restarted by the introduction of carbon dioxide into the respired atmosphere. But it would seem preferable to restore active respiration by removing the cyclopropane rather than by stimulating a deeply-depressed respiratory centre. This can be achieved by continuing rhythmic bag-compression with the absorber out, and periodically flushing through the closed circuit with air. There is an additional advantage in introducing air slowly towards the end of a major operation—particularly a thoracotomy, during which an atmosphere rich in oxygen has been used—as a debilitated patient may not satisfactorily tolerate a sudden change.

A difficulty may arise with abdominal cases, as maximal

relaxation is required for peritoneal closure shortly before the end of the operation. One solution to this problem is to inject rapidly a very small dose of short-acting barbiturate (e.g. pentothal 0.2 g.) immediately before the peritoneal edges are picked up, and to commence washing out cyclopropane immediately after the peritoneum has been sewn. But unless a proper balance has been arranged between volatile and non-volatile agents, and a correct assessment of respiratory depression has been made, there may be insufficient time during suture of the abdominal wall for the restoration of normal breathing. An embarrassing situation can occur in which one patient remains apnoeic at a time when the induction of another is due. The prevention of such occasions is the outcome of experience. The injection of analeptics in the usual dosage makes little lasting contribution to hastening the return of normal adequate respiration in such cases, and in the author's opinion the use of these drugs finds no place in the management of patients recovering from controlled-respiration anaesthesia.

In no circumstances should a patient be moved out of reach of the operating-room facilities for respiratory resuscitation before completely adequate spontaneous breathing has been re-established. This is particularly important in shocked patients and those who have been deeply anaesthetized. Vigorous stimulation with carbon dioxide can produce sufficient hyperpnoea to reduce the cyclopropane tensions in the higher centres to a level at which signs of partial consciousness reappear, though a considerable quantity of the gas remains located in other tissues. A false sense of security is created and the patient may be removed from the operating room at this stage. When, however, he is allowed to breathe normal air, the stimulus to respiration is removed and an apnoeic period follows, during which cyclopropane is re-distributed in the body and the higher centres become "re-anaesthetized". The attendant anoxaemia introduces an unnecessary hazard into the recovery period, and such events, though forming an interesting link between the theoretical aspects of the physiology of anaesthesia and the realities of clinical practice, are to be avoided. The use of carbon dioxide should be restricted to the production of momentary hyperpnoea at the end of the operation, and aimed at aerating the lung-bases after spontaneous respiration has been thoroughly re-established.

Controlled and Assisted Respiration with Agents other than Cyclopropane

Under ether anaesthesia, abdominal relaxation to a degree which satisfies all demands can be produced whilst active respiration is still effective and the need for controlled respiration does not arise. In some cases, however, following depressant premedication and barbiturate induction, or when ether is used for thoracic surgery, spontaneous respiration may be at times inadequate. In these circumstances, inspiratory movements can with advantage be augmented by suitably-timed bag-pressures. Momentary apnoeic periods, if offering surgical convenience, can be produced by hyper-ventilating in a similar manner through an efficient absorber.

Under pentothal anaesthesia, profound muscular relaxation is usually associated with considerable respiratory depression, and assisted respiration is of value. However, prolonged deep anaesthesia with pentothal alone has undesirable features, and balanced anaesthesia is generally considered preferable.

Should curare¹ be used in combination with inhalation anaesthesia to procure abdominal relaxation, the attendant intercostal paralysis may seriously impair respiratory efficiency. In such cases assisted or controlled respiration (depending on the degree of respiratory depression) will restore optimum ventilation and allow every advantage to be taken of the remarkable properties of this drug.

The employment of nitrous oxide with controlled respiration for thoracic surgery has been thoroughly discussed by Crafoord (1940), who describes a mechanically-operated device (to replace manual bag compression) used in conjunction with a continuous-flow nitrous-oxide/oxygen apparatus. He advises moderate hyperventilation, and apnoea due to lowered carbon-dioxide tension is a feature of this form of anaesthesia. Of the remaining agents in common use, chloroform may find occasional application with this technique (for controlling the effects of an open pneumothorax) on the occasions when diathermy is regarded as a necessity during thoracic operations in the presence of a bronchopleural fistula.

Commentary

The controlled-respiration technique greatly enlarges the clinical usefulness of cyclopropane, but this does not justify the use of this agent in cases more satisfactorily dealt with by non-inhalation methods, e.g. in the muscular patient requiring profound relaxation over a long period and for whom local or spinal analgesia is not contra-indicated.

Crafoord has pointed out that the muscles of respiration are put completely at rest during this type of anaesthesia.

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This is in complete contrast to the laboured movements and active expiration usually associated with semi-closed methods. The possible influence of each of these factors on the occurrence of post-operative pulmonary complications is worthy of investigation. Further blood-carbon-dioxide studies during controlled respiration would also be of interest.

In the present state of our knowledge it would seem that the minimal amount of anaesthetic which will produce satisfactory operating conditions is, in the majority of cases, the best amount to use. This is true for controlled-respiration anaesthesia, and inadvertent overdosage through failure to estimate depth correctly may be one of the causes of some of the untoward post-operative circulatory effects which have been attributed to cyclopropane in the past.

It may be urged that the production of respiratory arrest creates too wide a deviation from normal to commend itself for routine use. However, opinion is easily biased by recollection of the sinister significance of respiratory failure caused by the less-volatile agents administered by open methods. This technique is certainly eminently satisfactory in use. As to post-operative effects, its advantages and disadvantages are mainly bound up with the merits of cyclopropane itself, about which medical literature shows frequent favourable reports interspersed with occasional words of warning. Further investigation is necessary before a final assessment can be made. But there can be no doubt that efficient controlled respiration is wholly preferable to inadequate spontaneous ventilation, and offers an effective solution to difficulties which often arise from this cause during inhalation anaesthesia.

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THE ANAESTHETIST AND THE CARE OF THE SURGICAL CASE

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To-day there is an increasing emphasis on the rehabilitation of the patient after operation. The rapid return of the citizen to full activity is of the greatest importance to national economy, to the overcrowded hospital, and to the patient himself. This demands an increasingly high standard of surgical and anaesthetic care.

Advances in anaesthesia have inevitably resulted in more

complicated techniques, which tend to restrict the practice to whole-time specialists. The time wasted in travelling between widely-separated hospitals and clinics, and the small fees paid—together with the shortage of trained men—cause the anaesthetist to spend an unduly high proportion of his time in the operating-theatre. This has led to considerable technical skill, but at the expense of clinical interest. The concentration of his work under one roof may even add to the time actually spent in the theatre by the anaesthetist, who is denied the change of scene entailed by the ward and outpatient-duties of the surgeon.

The teamwork of the operating-theatre requires a full co-operation by extending this outside the theatre, with the anaesthetist taking a larger part in pre- and post-operative care, advantage would be taken of his special training in sedation, in the relief of pain, intravenous techniques, and in the administration of oxygen and other gases. This increased range of responsibility should then attract into anaesthesia more of the type of student who is needed if the speciality is to progress. Moreover the

¹ [See BMB 824 —ED.]

overworked surgeon, if competent help were available, should welcome the delegation of responsibility in the preparation and after-care of his cases. It is recognized that this involves closer study by the anaesthetist of many problems such as nutrition in its widest sense, the proper balance between rest and exercise, and the general consideration of the physiology—and pathology—of the surgical patient, before, during and after operations, nor should he neglect the psychological factors. Improvement in the care of the surgical case will follow the wider application of knowledge already gained and may be fostered by careful record keeping, follow-up schemes, and by regular staff-meetings as already practised in some centres.

I PRE-OPERATIVE CARE

Every anaesthetic involves a risk to the patient, it is during the pre-operative visits that this risk is assessed and that steps can be taken to forestall or reduce the complications of the operative and post-operative periods. These measures may take time and should be considered either before admission or at the first occasion when operation becomes a possibility. comparatively little can or should be done on the very eve of operation. The routine examination, the choice of pre-medication, and the selection of anaesthetic procedure have often been fully described, but this paper refers to some aspects which are beginning to receive greater attention.

a Exercise and Rest

Any patient confined to bed for more than a short time will be "out of training". His respiratory efficiency and cardiovascular and muscular tone will be reduced and he will not be at his best to withstand the combined effect of major surgery and anaesthesia. When, therefore, a patient has been kept in hospital for any length of time he should be as much as possible out of bed, and invaluable help can be provided by the physiotherapy department in arranging and supervising suitable exercises, especially those to encourage free ventilation of the lung-bases by intercostal and diaphragmatic movements. These should be continued as soon as possible after operation by the physiotherapist, who can thus secure the psychological benefits of an active participation by the patient in his own cure. In this connection there is a tendency to reduce the time spent in bed after operation and Powers (1944), in a paper entitled "The abuse of rest as a therapeutic measure in surgery", concludes that

' Prompt restoration of surgical patients to normal life is an essential feature of convalescent supervision. Early post-operative activity and walking provide manifest modifications in customary convalescent care by which the process of reconditioning may be largely eliminated and early rehabilitation achieved. The indications for such a programme are manifold. no contra indications are apparent in this study of 100 consecutive cases.'

Dock (1944) has drawn attention to "The evil sequelae of complete bed rest".

b Nutrition

Recently attention has been drawn to the part played by nutrition in convalescence. Hospital diets have been shown to be frequently inadequate especially in protein and vitamins. Of these protein is the more important, and is thought to

be a factor in wound disruption (burst abdomen), in increased oedema in wounds (a possible cause of obstruction of the stoma of an alimentary anastomosis), and in the delayed healing of fractures, of trophic ulcers and of liver-damage (Riegel, Koop, Grigger, Rhoads & Bullitt, 1945). Reduced intake, deficient absorption, increased utilization and loss, for example, in exudates, may all occur in disease and result in protein depletion. Moreover it has been shown (Riegel *et al.*) that although no specific cause can be detected, other than the operation itself, patients lose weight in the post-operative period. In view of this, and the fact that protein intake is likely to be reduced for some time after operation, every effort should be made to improve the patient's nutrition before operation by increasing protein in the diet and by avoiding any prolonged pre-operative starvation. A recent paper by Cuthbertson (1945) should be consulted.

Vitamin deficiencies are unlikely to arise in healthy people eating a mixed diet, but impaired appetite, vomiting, diarrhoea, dietary restrictions or institutional feeding may produce them. Deficiency of thiamin (vitamin B₁) may contribute to impaired gastric motility and anorexia which, in turn, may lead to a decreased intake of this vitamin. Because of the part it plays in carbohydrate metabolism, thiamin has been given with glucose in intravenous alimentations. Nicotinic acid, another of the B vitamins, is known to prevent some forms of mental deterioration and its lack is probably associated with some confusional states. Nicotinic acid deficiency may be precipitated by the administration of sulphaguanidine or succinylsulphathiazole (Hardwick, 1946), which inhibit biosynthesis of this vitamin in the gut. Deficiency in vitamin C (ascorbic acid) has been said to delay wound-healing, but experimentally extreme deprivation in men has not produced such changes. The most that can be said at present with regard to these substances is that deficiency may be harmful and, since they are not poisonous, their intake should be adequate.

With regard to vitamin K, it is possible to be more definite. This vitamin is needed for the formation in the liver of prothrombin, one of the substances concerned in blood-clotting. Vitamin K, which is fat-soluble, is not absorbed from the bowel unless bile is present, so that bleeding is to be expected in obstructive jaundice. Gross liver-damage may also interfere with prothrombin formation and be the cause of haemorrhage, here also the "prothrombin time" (Quick) will be increased (and is used as a test of liver-function), but in the latter case vitamin K will not be effective. Since vitamin K analogue is harmless, it is in practice usual to give 10 mg by injection for several days before operating on patients with obstructive jaundice. Should the tendency to bleed persist, it may usually be controlled by means of blood transfusion.

c Haemoglobin

While it is, in certain circumstances, possible and justifiable to operate on severely anaemic patients, there is general agreement that it is better to remedy the anaemia beforehand than to rely upon transfusion during or even after operation. Blood grossly deficient in haemoglobin cannot carry sufficient oxygen to maintain the myocardium or liver parenchyma in optimal condition, these and other structures should have the advantage of adequate oxygenation for some days at least before having to meet the extra demands of the operative and post-operative periods.

Anaemia evokes a compensatory increase in cardiac output and pulmonary ventilation, and the anaemic patient's reduced reserve may be insufficient in the event of respiratory depression, obstruction or circulatory failure. Should these occur, even to a degree which would be normally of little moment, the consequences are likely to be serious. Similarly a blood-loss which would be withstood when the initial haemoglobin level is normal may prove insupportable if the initial level is low.

Cyanosis, depending for its production on the presence of reduced haemoglobin, becomes clinically apparent only when the latter exceeds 5 g per 100 cm³. In severe anaemia, however, the total haemoglobin may be only 5 g per 100 cm³ (corresponding to about 30% haemoglobin), and cyanosis will never appear. Lesser degrees of anoxia may occur which, if not fatal, can produce irreparable damage to the central nervous system, depress cardiac function, and may enormously increase the vulnerability of the liver to anaesthetic or other agents and toxins. These effects are so serious that every effort must be made to prevent them. Since cyanosis is a reliable sign of anoxia only in patients with normal haemoglobin, and the fact of its failure to appear deprives those in attendance of a valuable sign of oxygenation, anaemia of any marked degree should be treated before operation.

Anaemia may, if time permits, be treated in appropriate cases by iron or liver, but transfusion is not infrequently needed. The value of a slow rate of administration is well recognized, not only does it permit the transfusion to be stopped before more than a small volume has been given in those cases of gross haemolytic reaction due to ill-matched blood, but it avoids overloading the circulation, which is of especial importance in children or in cases of cardiac or pulmonary disease. Here the transfusion of concentrated erythrocytes should be considered. We have come to realize, however, that we should replace blood as it is lost and maintain blood-volume during the operation, thus preventing the ill effects of haemorrhage on the vital organs.

During the last few years important new problems have been revealed by work on the Rh factor (see Taylor & Race, 1944). This antigen is present in about 85% of whites, 95% of negroes and 99% of Chinese. If patients not possessing this antigen (Rh negative) receive a transfusion of Rh-positive blood they may develop anti-Rh agglutinins, which will cause a haemolysis if further Rh-positive cells enter the circulation. This sequence of events may occur when repeated transfusions are given, the reactions are usually mild at first being perhaps manifested only by an absence of the expected rise in haemoglobin value after transfusion. If the significance of this sign be not appreciated the ensuing reactions may be expected to increase in severity and may finally resemble the haemolytic reactions of ABO incompatibility. The highest titres of anti-Rh agglutinins develop in Rh-negative women pregnant with an Rh-positive foetus and here violent reactions may occur. Hence ideally every repeated blood transfusion should be Rh-compatible and, failing this, careful watch must be kept for reactions. Women who are, or who have ever been pregnant, should in the light of present knowledge receive Rh-compatible blood. This involves either expert grouping or the administration of Rh-negative blood in such cases. The latter is, however, comparatively scarce. The theoretical possibility also exists that a single transfusion of Rh-positive blood might

sensitize an Rh-negative woman, in which case, should she have an Rh-positive child, it would probably suffer from haemolytic disease. Few people are, however, so easily sensitized (Callender & Paykoç, 1946).

II. IMMEDIATE POST-OPERATIVE CARE

The difficulty and interest of the induction and operative periods may be greater than that of the withdrawal stage but they are no more important. The safe return of the patient to consciousness, the release of his physiology from pharmacological control, is a weaning which needs and should have expert guidance. General anaesthesia tends to depress the respiratory centre, which is, however, stimulated by many operative procedures. When this stimulus ends, unless the agents have been withdrawn from the circulation, the depression may become marked.

Fortunately most operations become less stimulating toward the close, as for example, after the peritoneum is closed in abdominal cases, and an opportunity is given to lighten the anaesthesia. This should be done gradually, so as to avoid the persistence of a tissue-concentration higher than that of the blood, in which case any transient decrease in pulmonary ventilation might be followed by an unwanted deepening of anaesthesia. Similarly, the oxygen and carbon-dioxide level should be kept as nearly normal as possible during the administration, in order that the respiratory centre may not become apnoeic when the patient returns to atmospheric breathing. These two considerations call for caution in the use of carbon dioxide to effect the rapid de-etherization of a patient by forced breathing.

A sudden fall in oxygen tension should not be permitted after major procedures, and this may be avoided by gradually increasing the nitrous oxide, or by admitting air into the circuit, the latter having the advantage that the atmospheric nitrogen is much less quickly absorbed by the pulmonary alveoli than is nitrous oxide or oxygen, and thus delays any collapse behind the mucous plugs which may later obstruct the bronchi.

At this stage, and before the patient is moved, the upper airways should if necessary be cleared by aspiration, the volume and the purulent nature of the secretions is often unexpected, and an obvious potential cause of pulmonary complications. Similarly, and if indicated, before the withdrawal of an endotracheal tube a suction catheter may be passed into the main bronchi. This "toilet" and care of the respiratory tract at the end of operation is becoming recognized as a most useful measure in the prevention of chest complications. Should this be judged insufficient, and more especially in the presence of known lung disease, persistent secretions, cyanosis or poor circulatory state, a bronchoscope may be passed and aspiration repeated under direct vision.

When reflexes are still in abeyance, or their vigilance is dulled by the remaining anaesthetic or sedation, the patient will need protection from the danger of inhalation of secretions, blood, vomit and other foreign matter until all the anaesthetic agent is removed and the period of heavy post-operative medication is past. This is provided as far as possible by vigilant nursing-care, and by so arranging the patient that the mouth is directed downwards. This can be done after most operations by placing the patient in the

lateral position, which has the added advantage that the tongue and jaw tend to fall forwards away from the posterior pharyngeal wall, thus lessening the risk of respiratory obstruction

a Fluids

The present views on the post-operative administration of fluids include the following points. In the first place it is presumed that the pre-operative care of the patient has ensured that any shock, gross anaemia, dehydration or salt-depletion will have been corrected as far as is possible before operation. Chloride deficiency should be suspected when the patient has had vomiting, diarrhoea, or has had continuous gastric aspiration, and may be inferred from the absence of urinary chlorides as indicated by the failure of silver nitrate to produce a cloudy deposit when added to urine acidified by nitric acid.

Any blood lost during operation should be replaced at once, and ordinarily no further transfusion of blood should be needed except in the case of continued haemorrhage or fall in haemoglobin. In conditions resulting in marked haemoconcentration, with raised haemoglobin value and decreased blood-volume, the circulating volume should be increased by serum or plasma. These contain valuable protein, remain longer in the vessels, and have little tendency to cause oedema. They are more expensive than glucose or saline solutions, which are, however, free from risk of infective hepatitis¹. The use of acacia to provide solutions of higher osmotic power has been followed by liver damage, and the search for suitable solutions continues.

It has been shown (Coller & Maddock, 1940) that during an ordinary operation, up to 1-1½ litres of fluid are lost to the patient by various routes. Usually the patient will be able to drink sips within a few hours of operation, but since drinking may be restricted by nausea after a major operation or heavy "etherization", it is kinder to minimize the patient's thirst during the early post-operative period by the routine administration of a pint [about 0.57 l.] of tap-water per rectum before he recovers consciousness. This procedure may be repeated at intervals, and seems to be tolerated more easily than is a continuous rectal drip, but even so in many cases it cannot supply sufficient fluid or be continued long enough. It has however the great advantage that by this route it is not possible to overload the circulation with fluid and chlorides, a risk which is present—in children especially—with intravenous methods. It is useful in this connection to remember that the adult need for water is about 5 pints (2.8 l.) in the 24 hours, and for salt, as much as is contained in one pint (0.57 l.) of isotonic saline. Glucose is tolerated in large amounts, and since a 5% solution in distilled water is isotonic, 4 pints (2.25 l.) of this solution, sterile and pyrogen-free, together with 1 pint (0.57 l.) of isotonic saline may be given intravenously and

will meet normal requirements. Since 5% glucose in normal saline is hypertonic, its use may be followed by some phlebitis. In cases where fluids and chlorides are being lost by vomiting, or by gastric suction, or when large volumes of fluid pass into the bowel as in ileus, then the quantity given must be increased even up to an intake of 8 pints (4.5 l.) or more per day, of which $\frac{1}{3}$ to $\frac{1}{2}$ should be saline.

It is helpful if the intake by mouth, the intake by infusion, the amount lost by vomiting, and the urinary output are all entered on a fluid-balance chart and this, together with the specific gravity of the urine and its reaction to silver nitrate (vide supra), is usually sufficient guide (Atkins, 1944) and will serve to prevent overdosage, which on the whole is more harmful than a little dehydration. Similarly, since an excess of chlorides may not be eliminated by the kidney and may cause pulmonary oedema, it is probably wise to give too little rather than too much saline, and to use fluids such as 5% glucose or serum or plasma and to add saline only in such amounts as to ensure that chlorides are excreted in the urine in sufficient quantity to produce only a light, cloudy deposit on the addition of silver nitrate. When any doubt arises the plasma chloride should be estimated.

b Heat

The cold, pale skin of the shocked patient is now regarded as being due to peripheral vasoconstriction, which diverts the reduced blood-volume to the more vital organs. The production of a good skin-colour by applying heat defeats this defence-mechanism, and may be followed by a fall in blood-pressure and deterioration in general condition. Heat also increases the metabolism of the tissues, thus creating an increased oxygen-need which may deprive other more important tissues of oxygen and, in the case of vascular injury, may cause a demand which cannot always be met and which may precipitate gangrene.

Morphine given by hypodermic injection to patients with either surface vasoconstriction or peripheral circulatory failure is slowly absorbed, and unless this state of affairs be appreciated a second dose may be given. When the blood-flow at the site of injection increases after resuscitation, absorption will become complete and overdosage may result. Where this possibility exists, morphine can be given with greater safety and precision by the intravenous route.

III LATER POST-OPERATIVE CARE

a Pulmonary Complications

Major post-operative pulmonary complications have been closely studied during recent years. Veal & Van Werden (1937) have pointed out that while this more careful observation has resulted in an apparent increase in their frequency, the better prophylaxis and treatment have been followed by a fall in mortality from these causes.

Atelectasis is the most common, and, since it is the usual precursor of more serious complications, the most important. Occasionally the whole of a lobe, or even a lung, is collapsed. More often the areas affected are small and scattered fairly widely in the basal zones of one lung, or less frequently both. Clinically the onset is usually sudden, within the first 48 hours, with fever and tachycardia. There is some cough, but in this lobular form, unless very widespread, dyspnoea and cyanosis are not prominent features. The physical signs include varying degrees of dullness to percussion, weak

¹ The unusually long incubation period of up to three or more months has delayed the recognition of infective hepatitis as a sequel to the administration of blood or blood-derivatives. The causative virus is not destroyed by refrigeration, filtration or by any of the preservatives or antiseptics at our disposal. Moreover the pooling of transfusion fluids infects the whole bulk, dilution not reducing the effect of the virus. Thus the transfusion of blood from one donor is less likely to be followed by hepatitis than is the administration of pooled plasma or serum, though the latter is now being produced in smaller batches. It has been realized for some time in venereal-disease clinics that jaundice is transmitted by traces of blood in syringes and needles and that only sterilization by heat is effective. The use of carbolic spirit or other disinfectants is inadequate and the application of this knowledge to the preparation of syringes used for intravenous anaesthesia is overdue. The delay is in part, due to the difficulty and expense involved in the replacement of the popular Record type syringes by the more heat resisting all glass patterns.

air-entry, and at times bronchial breathing with some mediastinal displacement in unilateral cases. With massive collapse of one or more lobes the symptoms and signs, including dyspnoea, cyanosis, and mediastinal displacement, are more marked. The pathogenesis is considered to be the absorption by the blood-stream of the gases retained behind a bronchial plug of mucus. It is to retard this absorption that some gas such as atmospheric nitrogen, or less often helium, can be admitted at the end of the operation to the anaesthetic circuit in order to replace the too-readily-absorbable nitrous oxide or oxygen. While this is probably the main factor, it has been shown that ciliary activity can move a bronchial plug towards the larynx sufficiently powerfully to produce behind the plug negative pressures far greater than any normally recorded in the pleural cavity, and these are easily capable of causing collapse of the alveoli (Hilding, 1944).

The formation of the mucous plug is favoured by the presence of increased secretions in recent infections of the respiratory tract, in gross pulmonary disease, in heavy smokers, and perhaps in the indiscreet use of ether. The nature of the secretions is most important, and it is found that a small amount of tenacious mucus, as in chronic bronchitis, is more harmful than a larger but more fluid collection such as is found in bronchiectasis. On this account, many prefer hyoscine to atropine, and most consider the post-operative and repeated use of any belladonna derivative unwise. Should bronchospasm occur, a piece of mucus too small to obstruct a normal bronchus may form a plug, and if this be of tenacious consistency it may remain as a film across the bronchial lumen after its relaxation. Pentothal and cyclopropane both tend to cause bronchospasm. On the other hand, the bronchial dilatation which accompanies the use of ether more than compensates for the excess secretions produced. This may be one reason why the use of the so-called non-irritant agents has not been followed by any marked reduction in the number of atelectases.

In health, mucus is raised by the ciliary action alone (Negus, 1933). When secretions are excessive the cough-reflex is stimulated, often by the movement, due to the tidal exchange, of mucus to a different and more sensitive area of mucous membrane. After operation, the cough-reflex may be depressed during a prolonged recovery-period or by heavy sedation, but far more important is the effect of pain from the site of operation which restricts the movements of the diaphragm and intercostal muscles, and thus diminishes pulmonary ventilation. Moreover, the coughing is itself painful and tends to be voluntarily restrained and made ineffective. This is reflected in the high incidence of atelectasis after operations on the thorax and abdomen, particularly those near the diaphragm, which contrasts strongly with the rarity of this complication after operations elsewhere—particularly on the head and limbs.

Many points in prophylaxis have been suggested above. Breathing exercises supervised by a physiotherapist before operation and resumed post-operatively have been found a most useful routine in upper abdominal and thoracic surgery. The avoidance of operation in the presence of respiratory infection, and careful post-operative "toilet" of upper and lower respiratory passages as described above should be practised. Morphine, although it depresses the cough-reflex, is indicated in carefully individualized dosage

to relieve pain: by so doing it allows greater respiratory excursions and makes the clearing of the bronchi by coughing less painful. Intravenous novocaine may prove useful for this purpose.

Brock (1936) advocates that, when the patient is turned on his side and all pillows have been removed for attention to the skin of the back, the nurse, while supporting any operative incision on the chest wall or abdomen, should induce the patient to make purposeful coughs to raise any sputum. This may be more effectively carried out if preceded on the first few occasions by an injection of morphine. This manoeuvre is also the most effective means of treating the established condition, then it should be personally supervised by the anaesthetist or surgeon, who may, to save time, give the small dose of morphine intravenously and should encourage the patient, who is often apprehensive, to make the effort which is usually rewarded by the expectoration of tenacious mucus or mucopus.

If this procedure is unsuccessful or impractical, a Magill tube may be passed under local anaesthesia through the nose into the trachea, and a suction catheter may then be introduced to evacuate the secretions—the coughing evoked probably contributing largely to the success of the practice. Alternatively, bronchoscopy performed with the patient sitting up in bed is not difficult and the suction, being under direct vision, is likely to be even more effective. The relief given to the patient by these methods is marked and can be life-saving. Moreover it must be remembered that persistent atelectasis is probably not infrequently followed by infection with resulting purulent bronchitis and pneumonitis. Although these, in many cases, respond to chemotherapy, the dangers of pulmonary sepsis with resistant organisms are so grave that every effort at prophylaxis must be made. Nosworthy's paper "Bronchoscopy in the prevention and treatment of traumatic and post-operative pulmonary lesions" (1944) summarizes his views and practice and should be read.

The tendency of atelectasis to spread to fresh areas and to recur after treatment, is not unexpected in view of its pathogenesis. This point is emphasized by McGrath (1945), who teaches that the initial episode should be taken as a warning of possible recurrences and urges their prompt treatment along the lines suggested above.

Pneumonia after operations is now held to be usually the sequel to atelectasis. The treatment of this primary condition is not only important prophylactically, but should, modified in accordance with the patient's general state, be continued to promote re-expansion and to prevent the spread of collapse to fresh areas. In view of the long period during which atelectasis may persist, and the comparative rarity of pneumonitis following it, chemotherapy should be withheld until the latter occurs, and, in view of the toxicity or inconvenience of the drugs at our disposal, should not be employed prophylactically.

The possible role of pulmonary infarction in the causation of pneumonia is undecided. In addition to those cases due to peripheral thrombophlebitis, there is the pulmonary infarction which results from cardiac failure, especially in old people.

The inhalation of vomitus may follow operation on patients with a full stomach, and commonly results in a pneumonitis which not seldom progresses to abscess-formation. This may be the result of the delayed gastric

emptying which accompanies apprehension in some patients—more especially children. Impatience and the pressure of work have resulted in catastrophe in many outpatient departments. When it is essential to proceed, the stomach should be emptied—in children by an emetic and in adults by a tube—before anaesthesia. In cases of obstruction to the alimentary tract or of gastric or intestinal dilatation, where vomiting may be expected, to withhold gastric lavage and aspiration involves taking a risk, normally unjustifiable, at the patient's expense. Patients too ill for this procedure are possibly moribund for lack of it, and certainly too ill for general or spinal anaesthesia. Unorthodox techniques such as pentothal and curare may serve in specially skilled hands but, in general, few exceptions can be made with any safety.

b Thrombophlebitis

The intravascular clotting of blood in the veins is a serious, if relatively uncommon, complication after operation. The patient is not only exposed to the risk of pulmonary embolism, but may receive such damage to the circulation of the legs that oedema, pain and skin ulceration result in long-continued disability. The concern felt by the attendants communicates itself to the patient, and post-phlebotic neurosis is often an added complication.

The causative factors responsible for intravascular clotting are only partly understood. Many of these, such as age, sex, time of year, and the presence of malignancy, cardiac disease, anaemia, dehydration and immobilization, are concerned in thrombosis, both in patients after operation and in those on whom no operation has been performed. The higher incidence in those subjected to operation is associated with changes in the blood, of which the increase in blood-platelets and decreased clotting-time are the most easily estimated and most significant. From the clinical point of view, venous stasis, although in itself insufficient to cause clotting, is of the greatest importance. It is favoured by inactivity of the muscles of the leg, which normally by their contractions intermittently compress and so empty the adjacent veins. Stasis may also result from the constant pressure of a pillow under the knees or from tight bandages. The main veins of the abdomen or thorax, may be subject to pressure from without by ascites, abdominal distention or pleural effusion, or they may be distended by the back-pressure of cardiac failure. The negative inspiratory pressure in the thorax normally aids the venous return to the great vessels, and this will be adversely affected by the restricted pulmonary ventilation which may occur in disease and after operations.

Three main types of venous thrombosis after operation are described.

- 1 The *superficial thrombosis* following intravenous therapy—especially by hypertonic or irritant solutions—or of varicose veins, is seldom followed by serious consequences.
- 2 *Thrombosis in the deep veins* giving rise to tenderness in the calf and pain on dorsiflexing the foot is commonly accompanied by pain, fever, oedema and lymphadenitis, and the tenderness and thickening of the vein spreading up to Scarpa's triangle results in the fully-developed picture of *phlegmasia alba dolens*. The clot in this type of thrombosis is firmly anchored to the inflamed venous wall. The danger lies in the impairment of circulation, which may leave a painful,

swollen and ulcerated leg, rather than in the possibility of embolism.

- 3 The *third type of thrombosis* is not accompanied by much inflammation of the vein-wall, and is therefore relatively symptomless and is associated with a loosely-adherent clot. Here there is considerable risk of embolism when the patient becomes more mobile.

The aetiology suggests many points in prophylaxis, but the most important is probably early and frequent movements of the leg muscles to empty the deep veins of the calf and foot. These exercises can be performed in comfort and safety in almost every case, and seem more likely to be effective than the lifting of a rigid terrified patient into a chair on the first or second post-operative day. They can be combined with breathing exercises under the supervision of the physio-therapist, and should precede the early mobilization of the patient where this is not contra-indicated. The use of a knee pillow to maintain the so-called Fowler's position is unnecessary and should be avoided.

Where thrombosis has occurred in the past, or is judged likely to occur, the clotting-time should be estimated, and if this is found to be decreased, anticoagulant treatment by heparin or dicoumarin should be considered after operation. The use of these substances must be controlled by frequent estimations of the clotting-time, since, if this is too prolonged, bleeding from the wound may occur (Barker, Cromer, Hurn & Waugh, 1945).

Dicoumarin diminishes the production of prothrombin by the liver within 24-48 hours after oral administration. Herrmann, in an excellent account, "Venous thrombosis and pulmonary embolism" (1945), which should be consulted, and on which this note is largely based, recommends a single dose by mouth of 300 mg on the first day, 200 mg on the second day and 100 mg on each successive day until the prothrombin time exceeds 27 seconds. The subsequent dosage of dicoumarin should be varied to maintain this level at which venous thrombosis is most unlikely to occur. This drug has superseded heparin except where a rapid effect is needed, as in pulmonary embolism. Here, the administration of heparin, 300 mg in 1,000 ml. of saline by slow intravenous drip over 12 hours, is usually sufficient to prevent fresh clotting without affecting clots already formed. The clotting-time should be estimated and the heparin continued until the dicoumarin, which should have been given when heparin was started, takes effect.

Anticoagulant therapy is contra-indicated in any blood disease in which bleeding may be expected, in hepatic or renal insufficiencies, in active tuberculosis, nutritional deficiency, and in the presence of open wounds. In the event of haemorrhage or emergency operation, the prothrombin time may be reduced by a large dose of vitamin K analogue (60 mg) and a transfusion of fresh whole blood.

The treatment recommended for the established condition in the leg is immobilization for as long as the inflammation is active—usually for 2-3 weeks—with the leg raised (Barker & Counsellor, 1938). Every effort to dispel the oedema fluid before it becomes organized and produces irreversible changes in the tissues should be made (Zimmermann & de Takats, 1931). Undue immobilization of the patient, commonly due to "embolophobia", favours the formation of fresh, loose clots, both above the adherent clot in the affected leg and also in the veins of the other side. This risk may be minimized by exercising the remainder of

the body and by the anticoagulant drugs already described. Later, pain and oedema may sometimes be reduced by paravertebral block with 2% procaine as described by Leriche & Kunlin (1934), but most patients will require the support of an elastic bandage.

Pulmonary Embolism may be rapidly fatal, but is often preceded by smaller embolic incidents. The cause of death is probably not wholly mechanical but in great part due to the intense stimulation of abnormal reflexes in the autonomic nervous system. De Takats (1944) recommends the immediate use of atropine and papaverine, and the avoidance of morphine and digitalis which may accentuate these reflexes. He teaches that these drugs should be given at the first hint of embolism. 'Lest a small embolism should be the starting point of spreading secondary thrombosis, heparin and dicoumarin should also be given. Since the prognosis for any given case is so uncertain, and emergency operation can be expected to succeed only in very special circumstances, treatment for acute cases should rely on prophylaxis and the

use of antispasmodic and anticoagulant drugs. Pilcher (1938) recommends operation for the comparatively rare cases where embolism causes right-sided heart-failure with pulmonary oedema, which would otherwise prove fatal within a few hours or days.

CONCLUSION

At the outset of his career, the attention of the anaesthetist is focused almost entirely on the actual administration during operation. With increasing experience he should be able not only to provide satisfactory operating conditions for the surgeon, but also to keep constantly in mind the convalescent period and end-result. A prophylactic attitude can do much to prevent or minimize complications, and its cultivation is of the first importance. The application by the anaesthetist of a special knowledge of post-operative complications should benefit the patient, help the surgeon, and bring a wider interest to the speciality.

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HISTORY

827

AN OUTLINE OF THE HISTORY OF ANAESTHESIA, 1846-1900*

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The Preparatory Period

The discovery and final establishment of inhalation anaesthesia as an integral part of surgical practice was partly the inevitable outcome of scientific research, partly the result of vagaries of circumstance. Researches on pneumatic chemistry and the physiology of respiration during the seventeenth and eighteenth centuries prepared the way for Joseph Priestley's¹ discovery of oxygen (1774) and for Lavoisier's² elucidation of the nature of the respiratory process (1774-85).

The work of Priestley and Lavoisier found a practical application in pneumatic medicine—the therapeutic inhala-

tion of gases. Carbon dioxide, oxygen and hydrogen were chiefly used, but the vapour of sulphuric ether also was tried. Indeed Valerius Cordus, who, in 1540, gave the first unmistakable description³ of the preparation of ether, had suggested that drops of the liquid taken by mouth would loosen phlegm and ease stubborn coughs.

Therapeutic inhalation was principally studied by the brilliant circle of men whom Priestley had drawn around him at Birmingham. In 1792 Thomas Beddoes, formerly lecturer in chemistry in the University of Oxford, and by ties of friendship one of the Birmingham circle, decided that pneumatic medicine ought to be systematically and intensively studied and he began to canvass his friends for money with which to found a research institution. By 1794 the Pneumatic Institution was established at Clifton, Bristol, and James Watt⁴, the engineer (another of the Birmingham circle and one with a particular interest in pneumatic medicine since his young son was dying of phthisis) was busy designing apparatuses for generating and inhaling gases.

Davy's Researches on Nitrous Oxide

In 1798 Beddoes was looking for a superintendent for the Pneumatic Institution and when, during a summer holiday at Penzance, a friend introduced him to the eighteen-year-old surgeon's assistant, Humphry Davy, whose chemical researches undertaken on his own account already marked him as a student of brilliant promise, Beddoes offered him

*This article is based on a much longer study on *The development of inhalation anaesthesia with special reference to the years 1846-1900* by Dr Duncum, which is in the course of publication by the Oxford University Press for the Wellcome Historical Medical Museum.

the appointment at Clifton Once installed, Davy set to work to complete an investigation, which he had already begun, on the physiological effects of nitrous oxide In the course of many inhalations of the gas (greatly diluted with

FIG 1 NOTES BY HICKMAN (1823)

Experiment 1st
 March 18th Took a puppy a month old & placed it on a piece of wood surrounded by water over which I put a glass so as to prevent the access of atmospheric Air in ten minutes he showed great marks of uneasiness - at 12 respiration became difficult and at 17 Minutes ceased altogether, at 18 Minutes Took off one of the Ears which was not followed by hemorrhage Respiration soon returned and the animal did not appear to be the least sensible of pain in three days the Ear was perfectly healed
 2nd
 Four days after the same puppy was exposed to a decomposition of the carbonate of lime by sulphuric Acid In 1 Minute respiration ceased I cut off the other Ear which was followed by very trifling hemorrhage and as before did not appear to suffer any pain in four days the wound healed The day after the operation he seemed to require an additional quantity of food which induced me to weigh him and find he gained 9 1/2 Dr & 24 grains in 9 days
 3rd 19th - 26th
 Took the same puppy and proceeded as in Exp 1st and respiration was acted on in much the same manner I cut off the tail and made an incision over the muscles of the loins through which I passed a ligature and made it tight No appearance of uneasiness until the day following when inflammation came on and subsequent suppuration The ligature came away on the 7th day and the dog is remarkably increased in size and now perfectly well

EXPERIMENT 1ST

March 20th I took a puppy a month old and placed it on a piece of wood surrounded by water over which I put a glass cover so as to prevent the access of atmospheric Air in ten minutes he showed great marks of uneasiness in 12 respiration became difficult and in 17 Minutes ceased altogether at 18 Minutes I took off one of the Ears which was not followed by hemorrhage Respiration soon returned and the animal did not appear to be the least sensible of pain in three days the Ear was perfectly healed

2ND

Four days after the same puppy was exposed to a decomposition of the carbonate of lime by sulphuric Acid In 1 Minute respiration ceased I cut off the other Ear which was followed by very trifling hemorrhage and as before did not appear to suffer any pain in four days the wound healed The day after the operation he seemed to require an additional quantity of food which induced me to weigh him and I found he gained 9 oz 1 Dr & 24 grains in 9 days

3RD APRIL 6TH

I took the same puppy and proceeded as in Exper 1st and respiration was acted on in much the same manner I cut off the tail and made an incision over the muscles of the loins through which I passed a ligature and made it tight No appearance of uneasiness until the day following when inflammation came on and subsequent suppuration The ligature came away on the 7th day wound healed on 12th and the dog is remarkably increased in size and now perfectly well

air) Davy experienced its analgesic effects, both when he was suffering from headache and on the famous occasion when he was painfully cutting a wisdom-tooth This led him to suggest⁴ that "As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusion of blood takes place"

In 1801 Davy left Beddoes in order to take charge of the chemical laboratory of the Royal Institution in London Although he had been apprenticed to a surgeon and although he had stated that nitrous oxide might be used in surgery, after leaving Clifton he made no further attempt to interest the medical profession in his discovery and the profession itself ignored its significance

At the Pneumatic Institution, however, Davy had frequently induced others to inhale nitrous oxide, in order to study its effects, and both the subjects of these experiments and onlookers had derived considerable amusement from the antics which light intoxication with the "laughing gas" produced After he had taken up his duties at the Royal Institution, Davy continued to entertain visitors by letting them inhale nitrous oxide, and such inhalations became fashionable When in 1818, it was suggested⁶ (anonymously, though probably by Michael Faraday) that ether vapour would produce effects very similar to those of nitrous oxide, ether, too, was inhaled for amusement's sake

Pioneers of Inhalation Anaesthesia

Henry Hill Hickman

After studying the literature of pneumatic chemistry (although apparently not Davy's monograph on nitrous oxide), Henry Hill Hickman, a young Shropshire general practitioner, came to the conclusion that the inhalation of carbonic-acid gas would harmlessly obtund the pain of surgical operations During 1823 he proceeded to put his theory to the test in a series of minor operations performed on puppies, kittens and mice None of the animals showed any signs of pain during the removal of ears, tail or parts of limbs, all survived the ordeal without ill consequences (Fig 1)

Despite the success of these experiments, an account of which he published⁷ in 1824, Hickman hesitated to apply his discovery to human beings without first gaining the support of other medical and scientific men In this he completely failed, both in England, where he approached the Royal Society, and in Paris where, in 1828, he petitioned Charles X for the co-operation of the Academie de Medecine⁸

Crawford Williamson Long

In the early eighteen-forties ether and nitrous oxide "frolics" were still a popular form of entertainment in America, and after a demonstration of the effects of "laughing gas" in the State of Georgia, C W Long, a young general practitioner in the town of Jefferson, was asked by some of his friends to arrange similar demonstrations to while away the evenings Unable to obtain nitrous oxide easily, Long provided ether vapour In the course of these ether frolics Long observed that he and others under the influence of the vapour frequently bruised and scratched themselves when stumbling about, yet did not feel any pain This led him to think that surgery might be painlessly performed on etherized

subjects and in 1842 he proved this supposition correct when he removed three small tumours from the neck of a lad who had willingly consented to inhale⁹ During the next two years Long performed several other minor operations on etherized patients, but cases which Long thought suitable for such treatment were not frequent in his country practice, and although he meant to publish some account of his discovery when he had collected enough information, in fact he was forestalled by Horace Wells

Horace Wells

Wells was a dentist, living at Hartford, Connecticut and in December, 1844, at a demonstration of the effects of inhaling nitrous oxide, which concluded a pseudo-scientific lecture on the gas given by Gardner Quincy Colton, he made a discovery similar to Long's. He too, noticed that a youth who stumbled into a bench after inhaling, appeared unaware of having severely barked his shins and he, too, was led to think that surgical pain similarly might be obtunded. Accordingly, the next day Wells induced Colton to let him inhale nitrous oxide so that a colleague might extract a tooth from him. The success of this operation led Wells to adopt the use of nitrous oxide in his dental practice.

Early in 1845, having done 15 painless extractions, Wells arranged (through a former dental partner, William Thomas Green Morton) to give a demonstration at the Massachusetts General Hospital in Boston. Probably because the patient was a tough young student, because the bag of gas was too small and the inhalation too brief, the patient yelled lustily

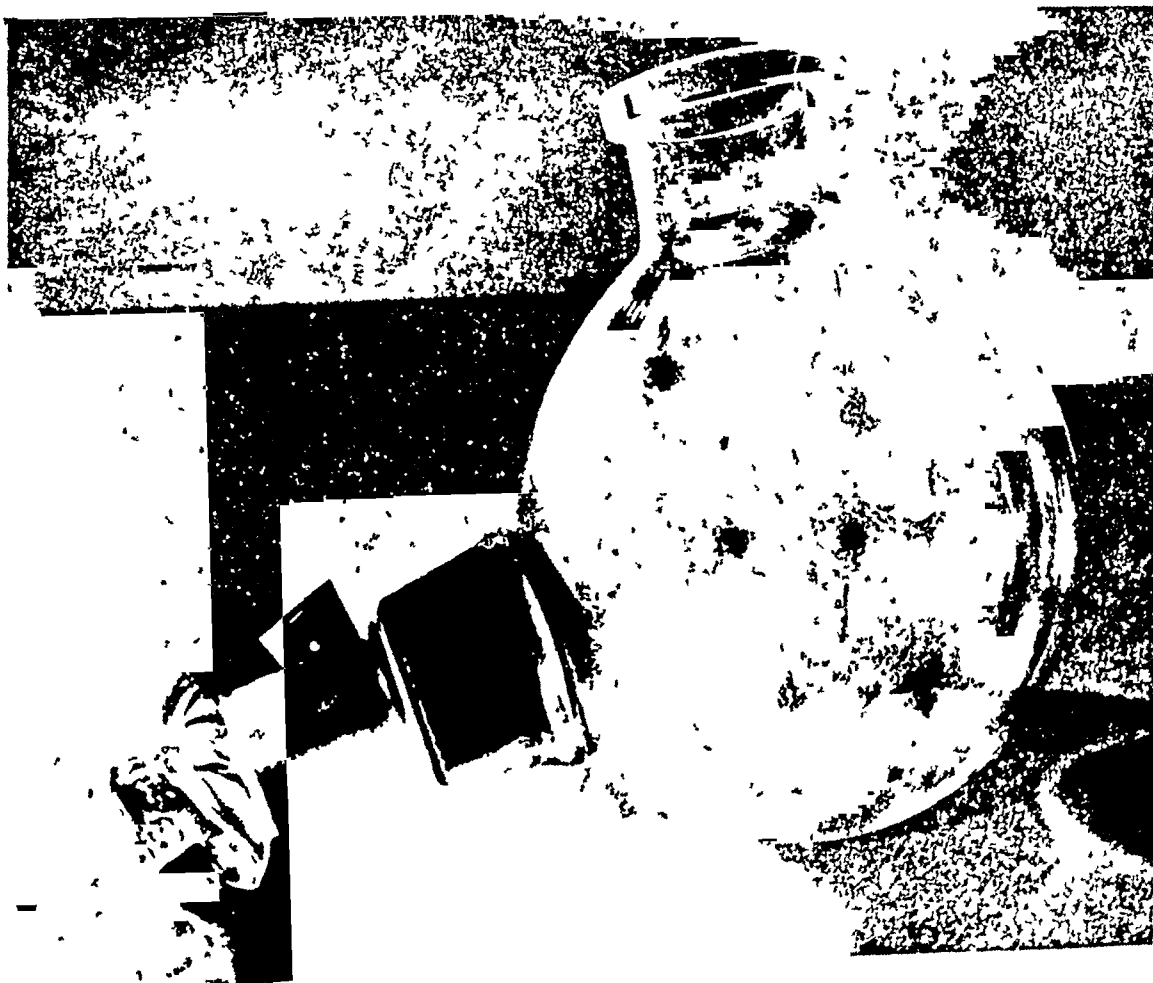
as his tooth came out, the audience scoffed and Wells was discredited!¹⁰

Morton and the Adoption of Surgical Anaesthesia

Profiting by Wells's experience, W T G Morton came to the conclusion that surgical anaesthesia was practicable, although not with nitrous oxide. The obvious alternative was ether vapour.

After spending much thought on the problem of how best to administer the vapour, and after obtaining a certain amount of sound advice, particularly that the ether used should be chemically pure, from the chemist C T Jackson, whose pupil Morton had once been, Morton succeeded, on 30 September, 1846, in painlessly extracting a tooth from Eben Frost¹¹. On that occasion the patient inhaled ether from a folded cloth.

Morton hastened to arrange another demonstration at the Massachusetts General Hospital. On 16 October, 1846, Morton—this time using a valved glass flask containing an ether-soaked sponge (Fig 2)—convinced the assembled surgeons that surgical anaesthesia could effectively be induced and maintained. The patient was not wholly unconscious during the operation—the removal of a tumour from beneath his jaw—but he afterwards said that he had suffered no pain and likened the feel of the knife to that of “a blunt instrument passed roughly across his neck”¹². Morton was lucky to have succeeded so well on this occasion, for he arrived in the operating theatre late and flustered and the inhaler which he used had been devised only during the past twenty-four hours and there had been no time to test its efficiency.

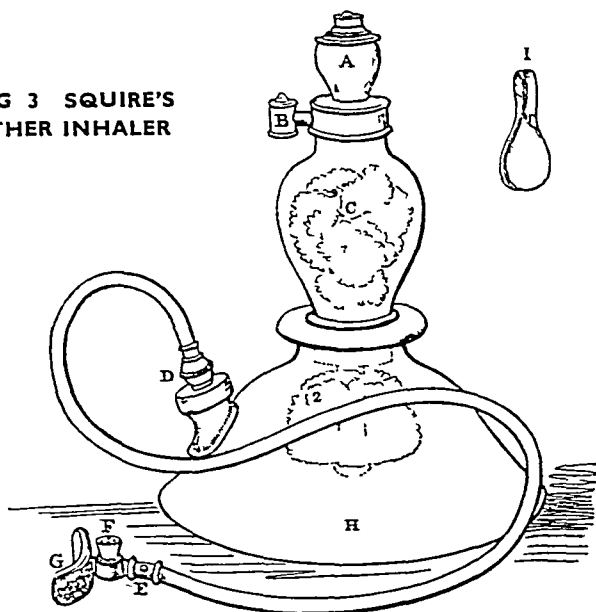


**FIG 2 MORTON'S
ETHER INHALER (1846)**

This flask, which is in the possession of the Massachusetts General Hospital in Boston, is said to be that actually used by Morton on 16 October, 1846. The metal cylinder connecting the globe to the mouthpiece formerly contained two leather flaps—one acting as an inspiratory, the other as an expiratory valve. The expiratory port lies beneath the protrusion just visible on the neck. The sponge is no longer kept inside the inhaler.

The Boston surgeons, however, were greatly impressed and the accounts of this demonstration which they gave to friends and colleagues, not only elsewhere in America but in the Old World, gained immediate acceptance for etherization in surgery

**FIG 3 SQUIRE'S
ETHER INHALER**



- A The Urn with its stopper, into which the ether is poured
- B Valve which admits the air
- C Contains sponge saturated with ether
- D Valve which opens at each inspiration, and closes at each expiration
- E Ferule for regulating the quantity of atmospheric air admitted
- F Valve for the escape of expired air
- G Mouth piece
- H Lower vase
- I Spring for closing the nose

The Use of Ether established in Europe

The news reached the physician Francis 'Boott¹³ at his house in Gower Street, London, in December 1846. It came from his Harvard friend, Jacob Bigelow, whose son Henry had just read the first scientific paper on etherization, in Boston. Boott immediately passed on the news to the surgeon Liston who, on 21 December, 1846, painlessly amputated a leg and removed a toe nail from two patients who had inhaled ether from an apparatus (Fig 3) improvised for the occasion by the Oxford Street chemist, Squire¹⁴.

In France, although news had come directly from America to one or two surgeons, it was not until January, 1847, after accounts of many successful cases had appeared in the English Press, that J F Malgaigne¹⁵ was emboldened to try etherization for himself. Others then followed his example and during the spring of 1847 most of the leading surgeons of Europe began tentatively to use anaesthesia.

Nearly all the early inhalers had certain serious imperfections in common. The glass flasks containing sponge often became so chilled through the vaporizing process that the process itself was progressively checked until the patient was breathing little more than ice-cold air—and that with difficulty—owing to the resistance offered by narrow tubing and imperfectly-acting valves. Moreover, he had to breathe through a small tube held between his lips, his nostrils being pinched together by an assistant or by a nose-clip. In these circumstances it was scarcely remarkable that the patient, instead of passing smoothly into unconsciousness, should have become so obstreperous that surgery was impossible¹⁶.

Although Morton's inhaler did not freeze up (because the administrator held it in his hand) and did not offer great resistance to breathing, its use was abandoned by the surgeons of the Massachusetts General Hospital in February, 1847, because Morton had applied for a patent for it. They adopted instead, the use of a bell-shaped sponge which, having poured plenty of ether on to it, they applied firmly

**FIG 4
ANAESTHESIA IN 1847**

An early photograph showing the administration of ether from a bell shaped sponge at the Massachusetts General Hospital in Boston Mass (1847)



over both nose and mouth, disregarding objections, vocal and physical, on the part of the patient¹⁷ (Fig 4). So successful did this method prove and so well suited to American conditions, that it persisted without serious rival until the close of the nineteenth century, the only modification of the original method being the enclosure of the sponge in a cone improvised from a folded towel

Ether superseded by Chloroform

Ether itself was blamed for difficulties really attributable to faulty inhalers, and as early as 1847 many people had begun to look for a more manageable agent. When, in November, 1847, James Young Simpson, professor of midwifery at Edinburgh, announced that he had found it in chloroform and described¹⁸ how it could be administered simply by pouring it on to a folded cloth (some of his colleagues used the patient's nightcap or the worsted glove of an onlooker), the use of ether was quickly discarded. Although it was not long before fatalities began to occur, so great were the disadvantages associated with etherization that no general return to its use was made.

In the United States¹⁹, however, where the practice of pouring ether on to a sponge had already proved its worth, and at Lyons and Naples²⁰, where also an effective so-called "closed method" had been found—that of pouring ether into an impermeable bag, the mouth of which was held firmly over the patient's nose and mouth—etherization was soon readopted. In Vienna²¹ mixtures of chloroform and ether, in which ether predominated, were preferred to chloroform alone.

England and the Development of Anaesthetic Apparatus

From the outset English anaesthetic practice was distinguished from that of other nations by two features—the use and development of automatically-regulating inhalers and



FIG 5 JOHN SNOW (1813-58)

Snow was the first to specialize in anaesthesia. In addition to the references in Dr Duncum's paper, a short biographical note on Snow has been included elsewhere (BMB 836)

John Snow



FIG 6 SNOW'S CHLOROFORM INHALER (1847)

The vaporizing chamber is shown in section

the employment of specialists to administer anaesthetics. Elsewhere the simplest possible means of administration were customary, and since the maintenance of anaesthesia was generally regarded as a necessary but uninteresting routine procedure, the task was relegated to a student or junior house officer.

Prominent both as a designer of apparatus and as the first specialist anaesthetist was the physician John Snow, of London (Fig 5). Immediately surgical anaesthesia had been generally adopted Snow saw that its physiological effects must be investigated so that clinical practice could be based on scientific principles. On the continent of Europe also, physiologists—notably Flourens,²² in Paris—investigated anaesthetic action, but they made no more than occasional suggestions to the clinicians, whereas Snow determined to devote his career not only to the study but to the practice of anaesthesia.

Having ascertained the volume of saturated ether vapour which a given quantity of air would contain at different temperatures, Snow, during the early months of 1847, devised an inhaler in which the temperature of the vaporizing chamber was so regulated by a water-bath that a maximum of 30% ether vapour was contained in the air drawn from the inhaler by the patient's inspiration. The anaesthetic mixture could be further diluted with air by turning aside the expiratory valve on the facepiece—the valved facepiece itself being an innovation of Snow's²³.

In November, 1847, Snow constructed, on a similar principle, a chloroform inhaler (Fig 6), which delivered what he considered to be the safe maximum of 5% chloroform vapour in the inhaled air²⁴. During the eighteen-fifties and early sixties this inhaler was taken as a model by the majority

of English anaesthetists. In 1867, however, F E Junker, a doctor of medicine of Vienna, then working in London, devised an inhaler in which a stream of air was driven by a hand-bellows over or through a container of liquid anaesthetic, the mixture passing to a loosely fitting semi-spherical facepiece with an expiratory port in the dome²⁵. This inhaler was originally intended for B W Richardson's recently-introduced bichloride of methylene, but it was quickly appropriated to the administration of chloroform and soon displaced other regulating chloroform inhalers. Another who departed from Snow's methods was Skinner, of Liverpool, who, in 1862, introduced the use of a small wire face-mask covered with fabric on to which chloroform was allowed to fall drop by drop from a specially adapted bottle²⁶. Both Junker's inhaler and, more especially, Skinner's mask became popular in Germany.

The Search for the "Perfect" Anaesthetic

As the number of deaths from chloroform mounted, more and more people, while continuing to use the drug for want of a better, anxiously awaited the discovery of some new agent combining potency and ease of administration with safety. A few people, notably Thomas Nunneley²⁷, of Leeds, and John Snow²⁸, undertook extensive researches in an attempt to find such a drug. For a short time during 1857 Snow thought that he had found it in amylene, but when two deaths occurred from its use in his own hands, he regretfully classed it, so far as safety went, as being superior to chloroform but still inferior to ether²⁹.

In 1864 a Chloroform Committee (nominated by the Royal Medical and Chirurgical Society of Great Britain) reaffirmed, as a result of fresh experiments, that chloroform was more dangerous than ether because it was capable of directly paralysing the heart's action, whereas the action of ether was primarily upon respiration, so that if an overdose were given artificial respiration would restore the patient. The committee maintained, however, that the clinical use of ether was impracticable, and suggested that the best way to avoid the dilemma would be to use mixtures of chloroform and ether in the hope that each drug might counteract the disadvantages of the other. Harley's ACE mixture, 1 part alcohol, 2 parts chloroform and 3 parts ether, was particularly recommended³⁰.

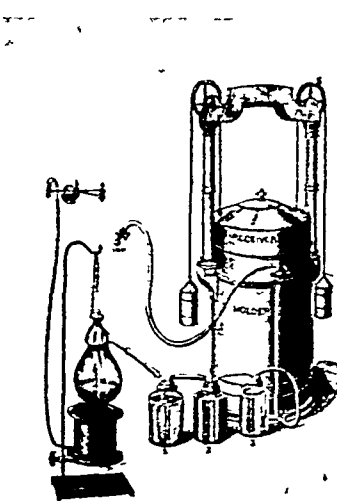
Although such mixtures did not immediately prove popular, despite the fact that an obstetrician named Robert Ellis devised a most ingenious inhaler for their use³¹, a few people took to inducing anaesthesia with chloroform and then changing to ether for maintenance. The committee's report marks the end in England both of the exclusive use of chloroform and of the hope that any one perfect, all-purpose drug could be discovered.

The Re-introduction of Nitrous Oxide into Dentistry

Although the Americans continued exclusively to use ether given by the towel-cone method in general surgery, in 1863 they readopted the use of nitrous oxide for dental surgery. This came about through G Q Colton, who had been the cause of Wells's use of the gas in 1844. In 1862 Colton was still travelling about the States describing and demonstrating the effects of nitrous oxide, when it happened that he was persuaded actually to anaesthetize an old lady for a dental extraction. This proved so successful that similar cases were undertaken and it occurred to Colton that

here was a much more satisfactory occupation than that of itinerant lecturer. In 1863, therefore, he founded the Colton Dental Association in New York³². During the International Exhibition in Paris in 1867 he taught the fashionable

FIG 7 AMERICAN COMBINED APPARATUS



The apparatus includes a generator, a gasometer and an inhaling tube for nitrous oxide anaesthesia (1863)

earliest days of etherization (Fig 7). Alternatively, gas was drawn off from the gasometer into a rubber bag from which the patient inhaled—the method Wells had used, although the bag was now larger. It immediately occurred to the London anaesthetists that these methods could be improved upon. During the course of the year 1868 nitrous oxide was compressed (first done by Faraday³⁴ in 1823) and made available in cylinders on a commercial scale³⁵. When the tap of the cylinder was opened, the gas flowed along narrow tubing into a reservoir bag (added to the apparatus at the suggestion of a dentist named Catlin) and thence it travelled along wide-bored tubing to a Snow's type of facepiece improved by J T Clover (Fig 8), who, after Snow's death in 1858, was acknowledged the leader of the anaesthetic profession. Clover also suggested the use of a small rebreathing bag attached to the facepiece, which could be brought in and out of use

American-born Parisian dentist, T W Evans, how to make and use the gas, and in the following year, 1868, Evans travelled to London in order to pass on the knowledge to the "chloroformists"³³.

The American method of administering nitrous oxide, demonstrated by Evans in London, was to store the generated gas in a counterpoised gasometer from which the patient drew it through a length of rubber tubing and a mouthpiece, his nostrils being pinched together as in the

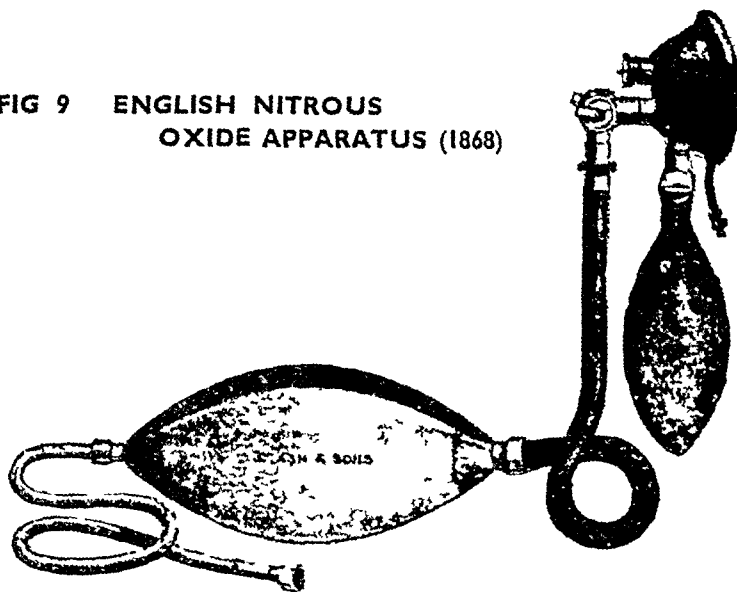
FIG 8 J T CLOVER (1825-82)



Clover was an early specialist in anaesthesia and his name has been perpetuated by the Clover inhaler (From an original photograph in the Nuffield Dept. of Anaesthetics Oxford)

as required, by means of a stopcock and adaptable valves (Fig 9)³⁶.

FIG 9 ENGLISH NITROUS OXIDE APPARATUS (1868)



Narrow tubing from the cylinder leads the gas into the Cattlin's bag. Thence it passes to a stopcock and facepiece from which hangs Clover's rebreathing bag.

The Use of Ether Revived in England

About 1870 one or two people in England made a tentative retrial of ether anaesthesia. Notable among these were J Warrington Haward, of St George's Hospital, London, and J T Clover, who was already experimenting with a nitrous-oxide-ether sequence³⁷. In 1872 B Joy Jeffries, an ophthalmic surgeon from Boston, Massachusetts, came to London to attend an ophthalmological conference. At the same time he was determined to convert the London "chloroformists" to the towel-cone method of administering ether. He arranged a series of demonstrations at various London hospitals where he folded up his towel with all possible dexterity, pushed a sponge into the apex, poured in a great deal of ether and clapped it down on to the patient's face, holding it firmly in place despite the victim's initial coughs and struggles³⁸. Tough as these methods appeared to the cautious English anaesthetists, they were undeniably successful. Soon they were being enthusiastically copied by professional anaesthetists not only in London but in the provinces³⁹.

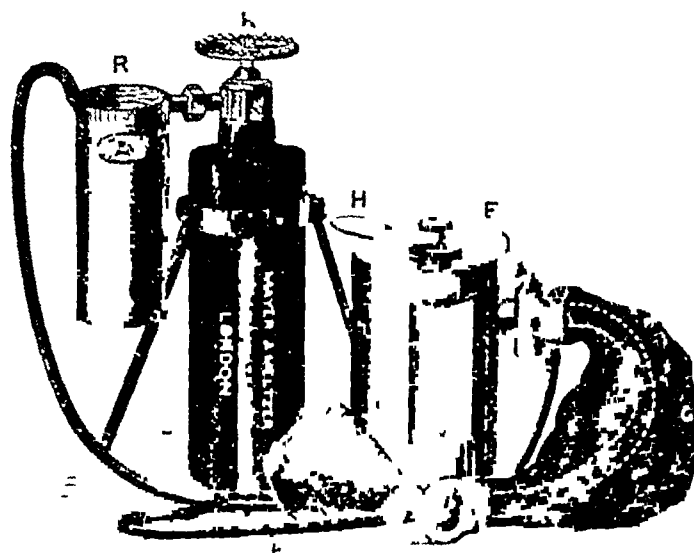
Once the use of ether was firmly re-established, however, the national preference for mechanical inhalers began to assert itself. Between 1874 and 1876 Clover⁴⁰, for example, was busy developing an apparatus which combined the pleasantness of nitrous oxide for induction with the safety of ether for maintenance (Fig 10). In 1877 he⁴¹ produced his portable regulating ether inhaler (Fig 11), on which his fame now chiefly rests, but which he himself considered merely as a second-best substitute for his gas-and-ether apparatus. Also in 1877 the surgeon L H Ormsby⁴² introduced his ether inhaler—a rubber bag attached to a facepiece with an adjustable air port, and in the mouth of the bag a cage containing sponge on to which the ether was poured (Fig 12). For many years Ormsby's ether inhaler rivalled Clover's in popularity.

Anaesthetic Development on the Continent

On the continent of Europe the development of nitrous oxide anaesthesia was interrupted by the Franco-Prussian War of 1870, and interest in it was not revived until 1878. Then the physiologist Paul Bert⁴³ suggested that instead of the usual method of administering nitrous oxide undiluted with air, which meant that asphyxial symptoms inevitably appeared, 50% nitrous oxide and 50% air should be administered under a positive pressure of two atmospheres. Bert's "anaesthetic car"⁴⁴, a mobile operating theatre in which surgeon, assistants and patient were alike subjected to increased atmospheric pressure, plied for a year or two between the hospitals of Paris, but was finally abandoned. Bert then proposed⁴⁵ the use of oxygen with nitrous oxide at normal pressure. This had already been tried by Andrews⁴⁶, of Chicago, in 1869. Neither the Americans nor the French showed much enthusiasm for such a mixture, and gas-and-oxygen anaesthesia was developed independently by the Russian obstetrician Klikowitsch⁴⁷, by various dentists in Austria and Germany, notably Hillischer⁴⁸, of Vienna, and finally by the specialist anaesthetist, F. W. Hewitt⁴⁹, in England, who greatly improved the apparatus for its administration.

No doubt because of the troubled times following the Franco-Prussian War, the revival of ether anaesthesia in England largely escaped notice on the Continent. The surgeon Julliard⁵⁰, of Geneva, discarded the use of chloroform for that of ether in 1877, however, administering it from a large, loosely fitting wire face-mask (Fig 13) with a rosette of flannel in the dome on to which the ether was poured, the whole mask being covered outside with waxed silk in order to exclude the external air^{*}.

FIG 10 CLOVER'S NITROUS-OXIDE-AND ETHER APPARATUS (1876)



The figure shows a cylinder with footkey (K) and expansion chamber (R). As an alternative to passing the gas through the bag (G) to the facepiece (F), it could be passed through the ether vessel (E) and down the tube indicated by dotted lines. The hook (H) enabled the anaesthetist to suspend (E) from his lapel. The regulating dial can be seen behind the facepiece.

* The administration of ether from a face mask (such as Schimmelbusch's) covered only with a few layers of permeable gauze was not widely practised until after 1900. This method was introduced by L H Prince⁵¹ in America about 1895, and was independently adopted by a few German surgeons about 1901⁵².

During the eighteen-eighties the Copenhagen surgeon Wanscher⁵³ introduced the use of ether—given either rectally or by inhalation—into Danish practice. His inhaler resembled Ormsby's except that there was no cage to hold a sponge, the liquid ether being poured straight into the bag, and there was no air port in the facepiece.

The use of Julliard's method spread northwards from

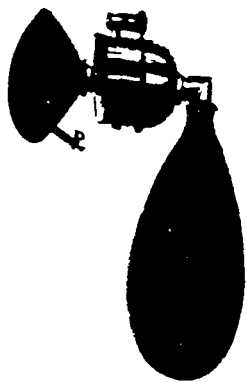


FIG 11 CLOVER'S PORTABLE REGULATING ETHER INHALER (1877)

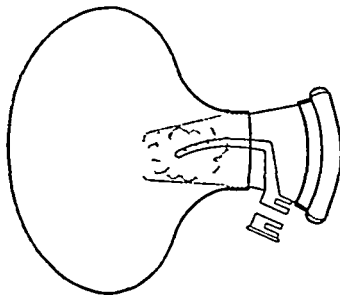


FIG 12 ORMSBY'S ETHER INHALER (1877)

Geneva and by 1890 had reached Tübingen in South Germany⁵⁴, at about the same time Wanscher's inhalation method was adopted by Landau⁵⁵ at his gynaecological clinic in Berlin.

At the Tenth International Congress of Medicine, held in Berlin in 1890, Professor Horatio Wood⁵⁶, of Philadelphia, read a paper stressing, with the aid of statistics, the far greater safety of ether anaesthesia as compared with that of chloroform. As a result of this paper the surgeon Gurlt, of Berlin, independently compiled statistics at the request of the German Surgical Society, and these succeeded in convincing German surgeons that etherization was worth retrial⁵⁷.

By about 1894 ether was being widely used in Germany and the surgical profession was divided into two factions—those who preferred Wanscher's inhaler and those who preferred Julliard's mask. By the close of the century, however, enthusiasm had waned, for many German surgeons had come to the conclusion that although ether was safer during the actual time of operation, its advantages were outweighed by the post-operative chest complications which appeared to them to be inseparable from its use⁵⁸.

In France a few surgeons, following the German example, revived the use of ether in and after 1895⁵⁹. Hitherto those surgeons who wished to minimize the dangers of chloroform had done so by adopting the 'mixed anaesthesia' suggested

by Claude Bernard⁶⁰ about 1869 and developed by the surgeons Labbe and Guyon⁶¹. This consisted in giving the patient a preliminary subcutaneous dose of morphine in order to prolong anaesthesia and at the same time reduce the amount of chloroform necessary.

During the late eighteen-seventies the belief became prevalent that inhibition of the heart's action so often observed during chloroform anaesthesia was due to stimulation of the vagus nerve by the drug. It was further believed that this danger could be averted by paralysing the vagi with atropine. In 1883 Dastre⁶², of Lyons, suggested adding the "protective" action of atropine to the advantages of morphine-chloroform anaesthesia, and he stated also that atropine would prevent the nausea caused by morphine. Premedication as it is known to-day developed only after 1900, however, as a direct outcome of Crile's warnings against the dangers of surgical shock.

The Development of Non-Inhalation Anaesthesia

Although immediately upon the universal adoption of anaesthesia during the winter of 1846-7, surgical operations were made more endurable and more easy of performance for the surgeon, nevertheless as time passed the patient's chances of ultimate recovery worsened rather than improved, owing to the steadily-increasing occurrence of various septic conditions classed together under the name hospitalism. A survey⁶³ made in 1861 showed that in the hospitals of Paris 3 out of 5 patients died from septic infection following amputation, while in London 1 out of 3 died.

FIG 13 JULLIARD'S ETHER MASK



The mask has a waxed silk cover. A folded towel held round the patient's face during induction further excludes air.

In 1867 Joseph Lister⁶⁴, then professor of surgery at Glasgow, began to publish accounts of operations performed under antiseptic conditions. The elaborate procedure which Lister at first thought necessary did not appeal to his fellow-countrymen, but German surgeons who, on the eve of the Franco-Prussian War had been studying foreign surgical methods, used Lister's antiseptic precautions during the war itself and found them so successful that they continued to use them⁶⁵. Gradually the antiseptic routine was modified until

by the eighteen-eighties it had been completely discarded in favour of asepsis by steam-sterilization

The stimulus which the treatment of battle-casualties had given to German surgery—already served by such able men as Langenbeck and Ernst von Bergmann—and the increasing control of sepsis, led during the eighteen-eighties to rapid progress in the field of visceral surgery. American surgeons, who were then closely observing German advances and had enthusiastically adopted aseptic methods, were not slow in developing visceral surgery on their own account.

As surgical procedure became more delicate, the fact became increasingly obvious both in Germany and America, that anaesthesia was a far more important adjunct than it had until then been considered, and many surgeons looked with envy at the English system of specialist administrators. During the eighteen-nineties, indeed, anaesthesia began to become a profession in the United States⁶⁶, but another approach to solving the difficulties of anaesthesia was already being made there, as well as in Germany, by the surgeons themselves preparing a painless operating field by local methods.

In 1884 the ophthalmic surgeon Carl Koller⁶⁷ reported his successful use of a solution of cocaine in anaesthetizing the cornea, and soon cocaine was being widely used, both painted on mucous surfaces and injected hypodermically. The method of infiltration anaesthesia, developed first by Reclus⁶⁸ in Paris about 1886 and then by Schleich⁶⁹ in Berlin about 1891, was the only one to become firmly established before the close of the nineteenth century. Nevertheless the American surgeon Halsted had already laid the foundations of regional anaesthesia when, during the winter of 1884, he dissected out the brachial plexus, having first blocked the nerve-roots in the neck with cocaine solution⁷⁰, and the neurologist Leonard Corning⁷¹, of New York, had shown in 1885 that spinal anaesthesia was practicable.

While in England a few surgeons interested themselves in these developments in non-inhalation anaesthesia, the specialist anaesthetist viewed them either with disapproval or with apathy. In the first place he considered, with some justification, that he was able to provide satisfactory operating conditions by inhalation anaesthesia, and secondly he was no doubt biased in that he could not straightway command the skill to practise the new techniques even if he wished.

The Anaesthetic Position at the Close of the Nineteenth Century

At the time of the jubilee of ether anaesthesia in 1896 and of chloroform in the following year, the anaesthetic position as a whole naturally came under review. It was generally agreed that progress during those past fifty years had not been in keeping with the enormous advance made when surgical anaesthesia was adopted in the first instance.

The Scots remained content with a simple but effective routine method of chloroform anaesthesia which had scarcely changed since Simpson introduced it. The English—as a result of the Hyderabad Chloroform Commissions⁷² of 1888 and 1889 were, at the time of the jubilees, once more hotly debating the rival merits of ether and chloroform, and although their methods of inhalation anaesthesia were the most highly organized in the world and their specialist administrators the most expert, nevertheless they had to admit that the training given to the non-specialist and occasional anaesthetist left much to be desired⁷³. On the continent of Europe the advantages of employing specialist anaesthetists were not recognized, and indeed many surgeons, following the German example, were seeking to replace inhalation by non-inhalation methods which they believed were proving superior and which enabled them to take sole charge of anaesthesia. In the United States a similar tendency to develop non-inhalation anaesthesia was evident, but there the need for intensively trained administrators was at last beginning to be appreciated.

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⁵⁶ *Trans Int Congr Med* (1890) 1, 133 & 141

⁵⁷ *Dtsch med Wschr* (1891) 17, 599, (1892) 18, 735

⁵⁸ See e.g. *Dtsch med Wschr* (1894) 20, 719-22

⁵⁹ *Bull Soc Chirurgie Paris* (1895) 21, 358-80

⁶⁰ Bernard, C (1875) *Leçons sur les anesthésiques*, Paris, 234

⁶¹ *C R Acad Sci, Paris* (1872) 74, 627

⁶² *C R Soc Biol Paris* (1883) 5, 242

⁶³ Simpson, J Y (1871) *Anaesthesia, hospitalism and other papers*, Edinburgh, 291

⁶⁴ *Lancet* (1867) 1, 326, (1867) 2, 95 & 353

⁶⁵ *Sanitäts-Bericht über die deutschen Heere im Kriege gegen Frankreich 1870-1*

(1890) Berlin, 3 (iii), 37 & 38

⁶⁶ *Med Rec N Y* (1897) 51, 574

⁶⁷ *J Amer med Ass* (1928) 90, 1742

⁶⁸ Reclus, P (1903) *L'anesthésie localisée par la cocaïne*, Paris

⁶⁹ Schleich, C L (1899) *Schmerzlose Operationen*, Berlin

⁷⁰ *Johns Hopk Hosp Bull* (1925) 36, 4

⁷¹ *N Y med J* (1885) 42, 483

⁷² *Lancet* (1890) 1, 149, 421, 486, 1140 & 1369

⁷³ *Practitioner* (1896) 57, 387-93

THE HUNDREDTH YEAR OF ANAESTHESIA

A Short Survey of Modern Anaesthetic Practice

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On 21 December 1846, a major operation was performed under general anaesthesia for the first time in England. After nearly a hundred years it seems appropriate to review the progress and present practice of anaesthetics in this country.

In London and in many of the larger provincial centres the work is done mainly by specialist anaesthetists. It is now a condition of appointment to the staff of a hospital attached to a school of medicine that one should be engaged solely in the practice of anaesthetics; it is recognized that, with advancing knowledge and consequent elaboration of technique, the highest standards cannot otherwise be reached. This is a comparatively recent development and there are many of the older anaesthetists who are also general practitioners. A few of these remain resolutely opposed to modern methods, but there can be little doubt that many of the recent advances in surgery have been made possible by these methods.

AGENTS

Ether

Of anaesthetic agents, ether—the first to be employed in this country—remains the most popular, though some anaesthetists have abandoned it entirely. I find there are still many cases in which its use is appropriate—in spite of some extravagant claims there is, as yet, no drug or combination of drugs that is universally applicable. It is no longer held that the inhalation of ether vapour is an important factor in the production of post-operative chest complications.

Chloroform

Chloroform is still used in some cases where there may be risk of explosion from the diathermy cautery. Some obstetricians prefer it for midwifery, although primary heart-failure is almost unknown, there is no good reason to suppose that pregnant women are less liable than others to the toxic after-effects.

Ethyl Chloride

Ethyl chloride is widely regarded as being unnecessarily dangerous, but it is still used, because of its rapid effect, for induction of anaesthesia in children and for short operations such as tooth-extraction.

Vinyl Ether

Vinyl ether (vinesthene) is not much used because of its high cost, though it is greatly superior to ethyl chloride in similar procedures. Some anaesthetists use a mixture of vinyl ether with ethyl ether which combines many of the advantages of each.

Trichlorethylene

Trichlorethylene (trilene) has been given an extensive trial¹ but is not generally accepted. Its high potency and low volatility make its use extremely economical and it has the advantages of being relatively non-irritant and non-inflammable. Cardiac irregularities are frequent² though, probably, unimportant and it may produce a marked tachypnoea—the respiratory rate may rise to 80 or 90 per minute. Muscular relaxation is poor, and it should not be used to produce deep anaesthesia. For light anaesthesia, used as an adjuvant to nitrous oxide, it is probably quite safe. Some deaths have been reported following its use in a closed circuit. Lethal decomposition-products resulted from its interaction with the hot soda-lime used to absorb carbon dioxide.³

Ethylene

Ethylene has not been used to any extent since the introduction of cyclopropane. Cyclopropane is widely popular and is especially suitable for intrathoracic and for upper abdominal surgery. It is not irritant to the lungs and can be used with a high proportion of oxygen and, being a marked respiratory depressant, it lends itself easily to the technique known as "controlled respiration".⁴ Following a period of over-ventilation of the lungs, at a suitable depth of anaesthesia, spontaneous breathing ceases, artificial respiration is then maintained by the anaesthetist and is timed to avoid interference with the actions of the surgeon. Normal breathing can be restored very rapidly, at will, by reducing the concentration of cyclopropane. Recovery of consciousness is as rapid as after nitrous oxide.

Nitrous Oxide

Nitrous oxide is the agent most commonly used for minor dentistry and for other minor operations in ambulatory patients—always with oxygen. Opinion is divided on its mode of use with more potent agents, such as ether, in major surgery. Some hold that its part is merely that of a vehicle for ether vapour and, accordingly, will reduce its concentration to equal parts with oxygen, others, including myself, feel that it can be made to play a much more important part, with consequent reduction in the quantity needed of the more toxic agents. We aim to produce a steady basal level of anaesthesia using, most commonly, about 85% nitrous oxide with 15% oxygen, and to vary the depth below this basal level by varying the concentration of ether. Nitrous oxide is now widely used, in the same way, as an adjuvant to intravenous anaesthetics.⁵ Its use in midwifery will be discussed later.

Barbiturates

Thiopentone (pentothal) has largely replaced hexobarbitone (evipan). Some anaesthetists use it for all types of operation including even upper abdominal and intrathoracic surgery. Others regard this as unwise because of the prolonged post-operative unconsciousness that follows the large doses required. Used with nitrous oxide and oxygen the necessary dose is halved and its scope thereby extended.⁵ In many

¹ [See *BMB* 823 in this number—Ed.]

² Barnes, C. G. & Ives, J. (1944) *Proc. roy. Soc. Med.* 37, 523.

³ McClelland, M. (1944) *Proc. roy. Soc. Med.* 37, 527.

⁴ [See *BMB* 825 in this number—Ed.]

⁵ Organe, G. & Broad, R. J. B. (1938) *Lancet* 2, 1170.

hospitals it is the practice to induce anaesthesia with thiopentone whatever the main agent is to be, a move that finds great favour with the patients. A firm of English manufacturing chemists has recently produced thiopentone by three different methods and the samples are now undergoing clinical trial. It is interesting to note that, although chemically indistinguishable, each shows slight pharmacological differences from the others and from pentothal. A new thiobarbiturate, kemuthal, is shortly to be described in the medical press. Although less potent than thiopentone, the course of anaesthesia and recovery is very similar and it appears to have some advantages, notably, less marked respiratory depression and a much reduced tendency to cause laryngeal spasm, which constitute the chief dangers with thiopentone.

TECHNIQUES

Ethyl chloride, ether and chloroform are frequently administered by the open drop method, using a Schimmelbusch type of mask. The Nuffield Department of Anaesthetics has produced a device, the Oxford Vaporizer, which is calibrated to deliver known proportions of ether vapour, up to 25%⁶. As generally used, air is drawn by the patient's inspiration across the surface of liquid ether. The ether is maintained at a constant temperature by a water-bath, buffered by an intervening layer of hydrated calcium chloride crystals which melt at 29° C. This represents a great advance on any other method of administering ether and has proved especially valuable for battle casualties.

Most inhalation anaesthetics are given with a nitrous oxide-oxygen-ether apparatus, some form of which is now available at hospitals throughout the country. The gases are supplied from cylinders attached to the apparatus or, in some of the more modern hospitals, are led by pipe-line from a centrally-situated battery of large-capacity cylinders. In such institutions oxygen is laid on to each ward, and there is available also a supply of nitrous oxide which may be required for the performance of painful dressings. The gases are measured by flowmeters—the Rotameter is the present favourite and seems to be sufficiently accurate—one each for nitrous oxide and for oxygen and one for carbon dioxide or cyclopropane. In the standard type of apparatus there are two bottles through which the gases can be passed, one containing ether and the other chloroform, trilene or vinylene-ether mixture.

Carbon-dioxide-absorption

Closed-ether anaesthesia without absorption of carbon dioxide has largely been abandoned as undesirable and archaic. The carbon-dioxide-absorption technique is widely used, having been developed mainly since the introduction of cyclopropane, the high cost of which made some closed system essential to avoid waste. It is extremely economical in use and is particularly valuable in districts where supplies of anaesthetic gases are not readily available. It also makes it possible to employ inflammable anaesthetics in cases where the surgeon is using the diathermy cautery. The warmth and moistness of the inspired gases make an appreciable contribution to the prevention of operative shock. Carbon dioxide is absorbed in a canister of soda-lime which may be placed close to the patient's face or, in the circuit type of

apparatus, is mounted on the anaesthetic trolley. There are two main types of closed circuit apparatus manufactured in this country—the M I E (Medical and Industrial Equipment, Ltd) and the Coxeter-Mushin (A. Charles King, Ltd). Both are very efficient.

Tracheal Intubation

There have been no important recent changes in the technique of tracheal intubation. There is a widespread tendency, with which I do not agree, to use the oral rather than the nasal route where possible, on the ground that a tube of larger calibre can then be employed. Some anaesthetists intubate the trachea on all possible occasions, to ensure a free airway. This is an abuse of the method, it is better to restrict it to maxillo-facial, intracranial and throat-and-nose surgery where the anaesthetist has not free access to the head, to cases where there is danger of blood, pus or vomitus passing down the trachea, and to intrathoracic surgery. For nose and throat operations the addition of a pharyngeal pack gives full protection, where, as with intestinal obstruction, profuse vomiting may be expected or where an air-tight fit is needed for closed-circuit anaesthesia a tube is used provided with a rubber cuff which can be inflated in the trachea.

Local and Regional Block

There has been a revival of interest in local and regional nerve block following its adoption by anaesthetists. A bilateral intercostal nerve block, usually combined with light general anaesthesia, has been found especially valuable for difficult upper-abdominal operations. Using amethocaine (decicaine) or nupercaine, anaesthesia and muscular relaxation last well over three hours. The latest development is the bilateral vagal nerve block at its point of emergence from the skull⁷. Although complicated by the fact that the glossopharyngeal nerve is commonly involved, it is likely to prove of value for such operations as laryngectomy. Extradural block by the method of Dogliotti has been tried,⁸ but it is generally felt that its advantages do not compensate for the risks involved. Extradural caudal block is used by James, Galley⁹ and some others and can be employed even for upper-abdominal surgery.

Spinal Block

Spinal anaesthesia has its antagonists and protagonists, both groups holding extreme views, but, in general, it is less frequently employed than before. Nupercaine is the drug of choice, though amethocaine and procaine (novocaine) are preferred by some anaesthetists. Great concern has been caused by the occurrence of a number of cases of meningitis, many fatal. Some have been shown to be due to gross faults of technique, but others remain obscure.¹⁰ Continuous spinal anaesthesia has been used by Lee.¹¹

GENERAL CONDITION OF THE PATIENT

Much has been learnt about the treatment of wound shock and the prevention of operative shock—work that is falling more and more within the province of the anaesthetist—as a result of experience with battle casualties and air-raid

⁶ Mushin, W. W. (1945) *Proc. roy. Soc. Med.* 38, 308.
⁷ Dawkins, C. J. M. (1945) *Proc. roy. Soc. Med.* 38, 299.
⁸ Galley, A. H. (1945) *Proc. roy. Soc. Med.* 38, 303.
⁹ [But see *BMB* 822 in this number—Ed.]
¹⁰ Lee, J. A. (1945) *Proc. roy. Soc. Med.* 38, 115.

* [See Figure in *BMB* 829—Ed.]

casualties. Emphasis is laid upon the restoration of circulating blood volume by intravenous infusion of serum, plasma and blood, which is thought to be more effective than the injection of stimulant drugs in shock. The same measures are now used more frequently to prevent or delay shock in severe operations, a slow drip transfusion of blood is the rule in major thoracic surgery. I have given as much as five litres of blood during a transthoracic gastro-oesophagectomy for a carcinoma that would, until recently, have been considered inoperable. It seems probable, with advancing knowledge, that a time may come when no operation, within the competence and the endurance of the surgeon, will be thought impossible even on a patient in poor condition. It is not thought that the choice of anaesthetic agent in a patient suffering from shock is as important a factor as the skill and experience of the anaesthetist, but it is best to keep general anaesthesia at as light a plane as possible, using free injection of local anaesthetics to produce any necessary muscular relaxation.¹⁴

SPECIAL APPLICATIONS

Plastic Surgery

All major plastic surgery is undertaken under general anaesthesia, with tracheal intubation where indicated by the site of operation. Recent severe injuries to the lower jaw present a difficult problem as the airway is often already partly obstructed and will become completely so with loss of consciousness. In such cases it has been found best to give a rapid injection of one gramme or more of thiopentone—in otherwise fit patients—to clear the throat of blood or debris under direct vision down a laryngoscope and then to pass an endotracheal tube with an inflatable tracheal cuff. Anaesthesia is maintained in the usual way.

Nose and Throat Surgery

Tracheal intubation is also the rule in nose and throat surgery, including tonsillectomy, except in very young children. Intravenous anaesthesia for such cases, without intubation, is considered dangerous because of the risk of aspiration of blood. Bronchoscopy is performed under local anaesthesia in adults, sometimes with thiopentone as well. For oesophagoscopy general anaesthesia is preferred, after some alarming experiences with thiopentone, which have been shared by others, I feel it is wisest to use an oral endotracheal tube. Some anaesthetists use regional block anaesthesia for operations on the maxillary antrum, apparently with great success.¹⁵

Intrathoracic Surgery

Spinal anaesthesia has been tried for intrathoracic operations and abandoned because of the great fall in blood-pressure. For lobectomy and for operations on the heart or main arteries, it is customary to use an endotracheal cuffed tube, where, as with bronchiectasis, there is much secretion, this is aspirated from time to time through a catheter passed down the tracheal tube. For pneumonectomy endobronchial intubation is convenient as, by this means, the affected lung is completely shut off. Some anaesthetists use, instead, a catheter fitted with an inflatable rubber cuff which is passed down a bronchoscope into the main bronchus

of the affected lung.¹⁴ The bronchoscope is then withdrawn, the cuff inflated, and an ordinary cuffed tube passed, beside the catheter, into the trachea with the aid of a laryngoscope. This method can be used for lower lobectomy, the endobronchial cuffed catheter being passed beyond the opening of the upper lobe bronchus. Controlled respiration is maintained under cyclopropane anaesthesia or, more rarely, with thiopentone. Thoracoplasty is performed, usually, under local anaesthesia composed of brachial plexus block, intercostal or paravertebral block and local infiltration of the line of incision.

Children

It is considered important, where possible, to employ some form of basal narcosis before anaesthesia in children over one year old. Hexobarbitone, thiopentone, paraldehyde or bromethol (avertin) are given per rectum, or pentobarbitone (nembutal) or seconal by mouth. Nitrous oxide with oxygen and minimal quantities of ether is entirely satisfactory for maintenance of anaesthesia, even in very young children, but requires more than usual care as the margin between anaesthesia and anoxia is small.

Midwifery

For midwifery there are almost as many methods as there are practitioners.¹⁵ The most important drugs in use are omnopon, scopolamine, pethidine (dolantin, demerol), pentobarbitone, trilene, chloroform and nitrous oxide. My own preference is for pethidine in the early stages of labour, nitrous oxide intermittently in the later stages and cyclopropane during the actual birth. Midwives are allowed to use nitrous-oxide air in fixed proportions and the apparatus designed by Minnitt for this purpose has proved of value.¹⁶ Galley and some others are ardent advocates of extradural caudal block.¹⁷ For caesarean section, general anaesthesia with cyclopropane or nitrous-oxide-oxygen-ether is usual. Intravenous anaesthesia has been used¹⁸ but leads to more frequent stillbirth, partly because of foetal respiratory depression and partly because the increased uterine irritability may lead to delay in delivery. Dogliotti's extradural block has been used by pupils of Dawkins. The suitability of spinal anaesthesia for delivery by any route is a matter for dispute that is, as yet, unresolved.

RESEARCH AND TEACHING

Interest in research was stimulated by the foundation in 1937 of a chair of anaesthetics at Oxford University, occupied by Prof R R Macintosh. Among other matters his work has included the development of the Oxford Vaporizer, a new laryngoscope, intravenous morphine, alcohol and ether anaesthesia, intrasternal drip anaesthesia with avertin, and various techniques of regional nerve block, including vagal block. Investigation of post-operative complications has been helped by the publication by Nosworthy of a combined anaesthetic chart and record card, which is now in general use.¹⁹

An important recent development has been the use of d tubocurarine chloride in anaesthesia, which is discussed else-

¹⁴ Magill I W (1935) *Brit J Anaesth.* 13 92

¹⁵ Elam J E, Claye A M & Read, G D (1943) *Proc roy Soc Med* 36 523

¹⁶ Minnitt, R J (1943) *Proc roy Soc Med* 37 45

¹⁷ Galley, A. H. & Peel J H (1944) *Proc roy Soc Med* 37 650

¹⁸ Gille, L. C. & Quayle G (1940) *Proc roy Soc Med* 33 621

¹⁹ Nosworthy M D (1945) *Curr Res Anesth* 24 221

¹⁴ Organe G (1942) *Med Pr* 208 397

¹⁵ Dale L (1945) *Proc roy Soc Med* 38 624

where in this number²⁰ This is a preparation of one of the alkaloids of crude curare, which has been tried by a number of anaesthetists In suitable doses it produces profound muscular relaxation and its use, combined with light general anaesthesia, promises to be the most revolutionary advance of a century. The cardiovascular system is unaffected and there is a remarkable freedom from operative shock after even the most drastic procedures It is, unfortunately, in very short supply and must remain for some time in the experimental stage

Undergraduate teaching consists of lectures and demonstrations and of the administration, under supervision, of at least twelve anaesthetics A series of eleven films on anaesthetics, suitable for undergraduate students, has recently been completed at the Westminster Hospital²¹ Courses of

postgraduate lectures and demonstrations are organized by the Fellowship of Medicine at Oxford and in London and are attended by candidates for the Diploma in Anaesthetics Possession of this diploma is regarded as a minimal qualification in the specialty It is probable that a higher degree will be instituted in the near future.

* * *

It is difficult, in a short paper, to give more than a very superficial account of the practice of anaesthetics in Great Britain It can be said that interest in this branch of medicine has never been more lively and that we hope, in the near future, to make great strides towards the perfection of our art The extension of the duties of the anaesthetist to include all forms of resuscitation and many aspects of post-operative care will, it is hoped, attract a better class of recruit than has sometimes been forthcoming in the past

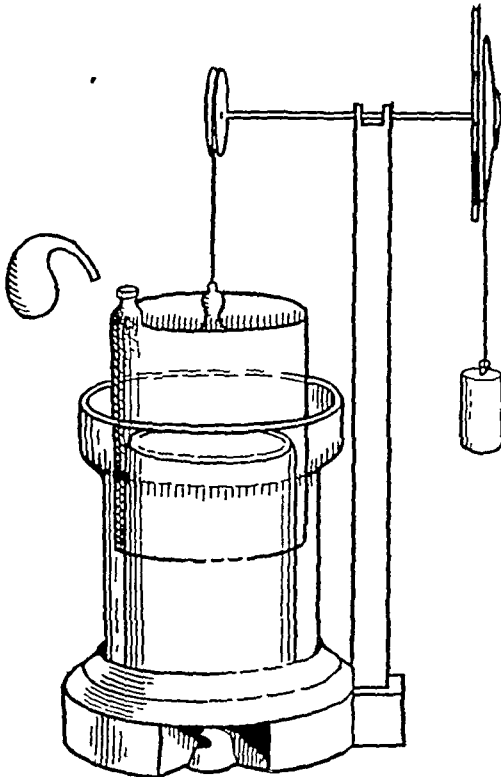
²⁰ [See BMB 824 —Ed]

²¹ [See BMB 848, in this number —Ed]

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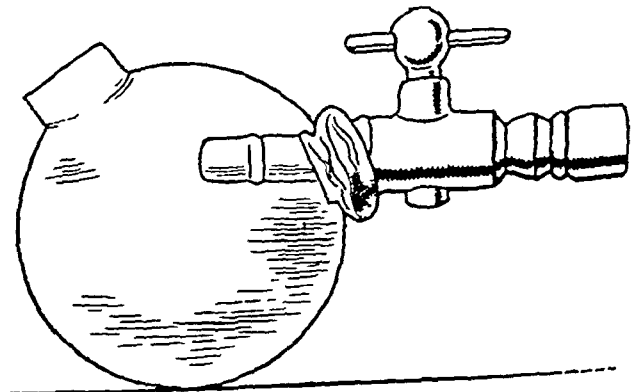
THE EVOLUTION OF ANAESTHETIC APPARATUS

A Brief Pictorial Survey. A CHARLES KING



1799 HUMPHRY DAVY'S GAS INHALER This comprised a miniature gasometer connected to a silk bag and is believed to have been used in 1800 by William Allen, lecturer in chemistry at Guy's Hospital, to demonstrate the loss of sensation to pain after inhalation of nitrous oxide

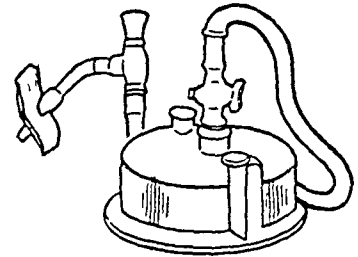
1846 SQUIRE'S ETHER INHALER Robert Liston performed two operations at University College Hospital and to both patients ether was administered by Peter Squire chemist of London, who had devised an inhaler consisting of a glass body with a brass top [This apparatus is shown in BMB 827, Fig 3]



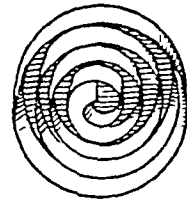
1846 MORTON'S ETHER INHALER. During an operation performed by Dr J C Warren in the Massachusetts General Hospital, Boston, Morton administered ether to the patient, using his inhaler, which consisted of a glass container into which was inserted a wooden tube with tap [See also BMB 827, Fig 2]



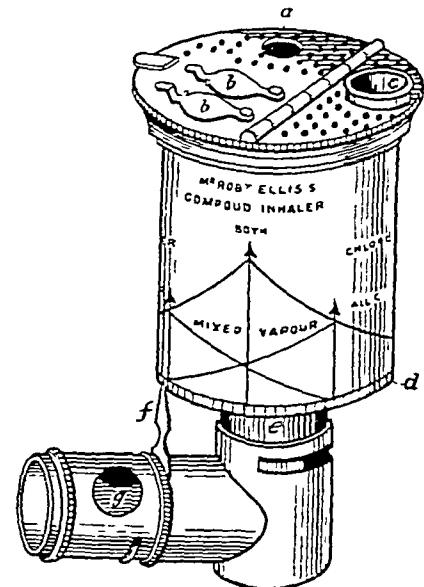
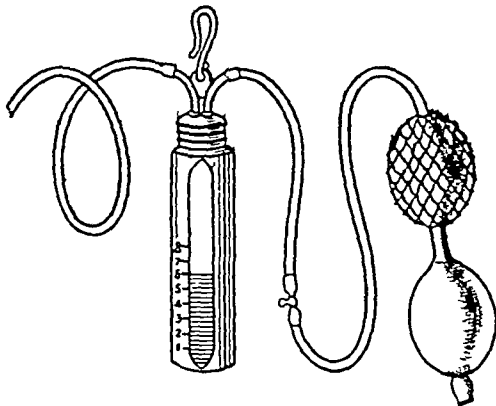
1847 SNOW'S CHLOROFORM INHALER. An outer metal cylinder for cold water surrounded an inner cylinder pierced with numerous air-holes and containing two coils of stout bibulous paper. Air slots were cut in the paper and sufficient chloroform only to permit clear passage was poured in. The facepiece was of leather or sheet-lead, with inspiratory and expiratory valves.



1847 SNOW'S ETHER INHALER. Ether vapour was inhaled by the patient through a mouth tube fitted with cedar-wood ball valves. Air was admitted to the vapour at one side of the apparatus and drawn over and round the spiral chamber depicted. This apparatus was used at St. George's Hospital.

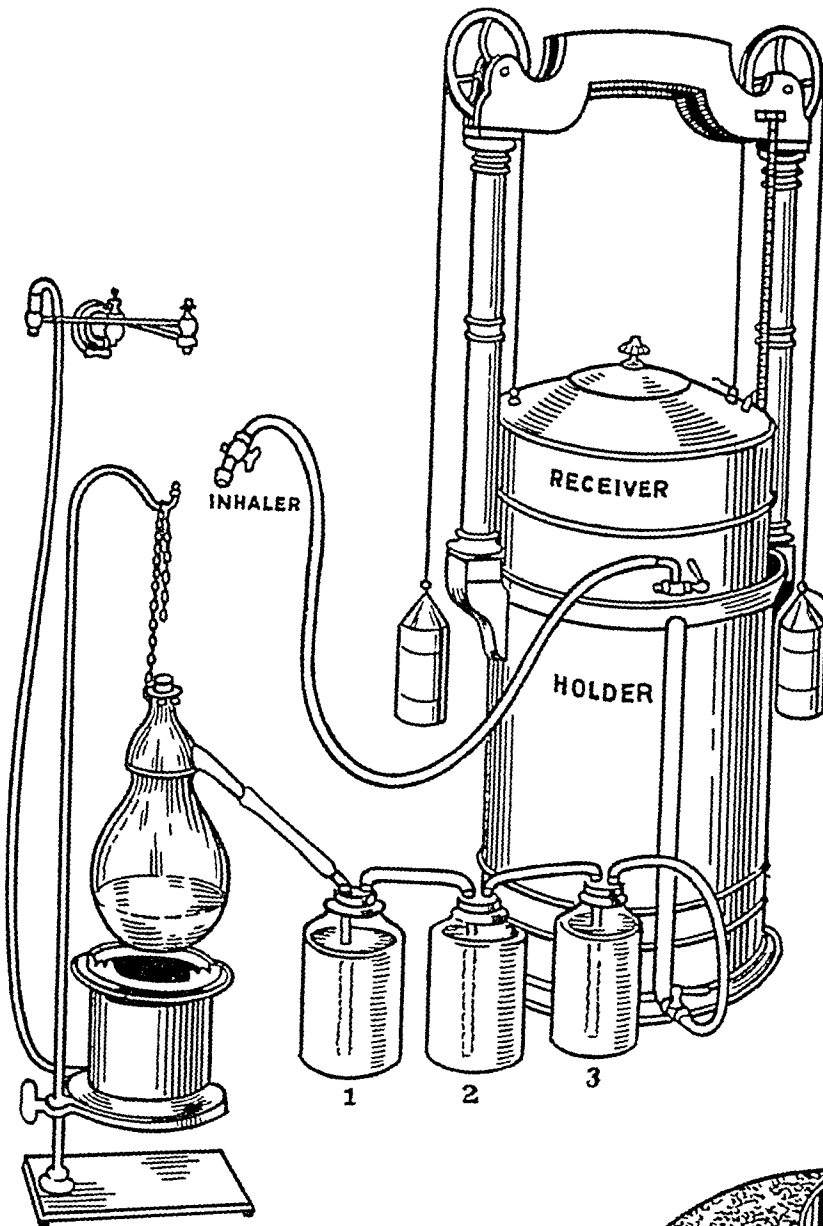


1862 CLOVER'S CHLOROFORM BAG INHALER. A mixture of thirty to forty minims of chloroform for every thousand cubic inches of air was pumped into a bag of known capacity, which when full allowed for several administrations. The facepiece contained control valves to give either air or a mixture of air and chloroform vapour.



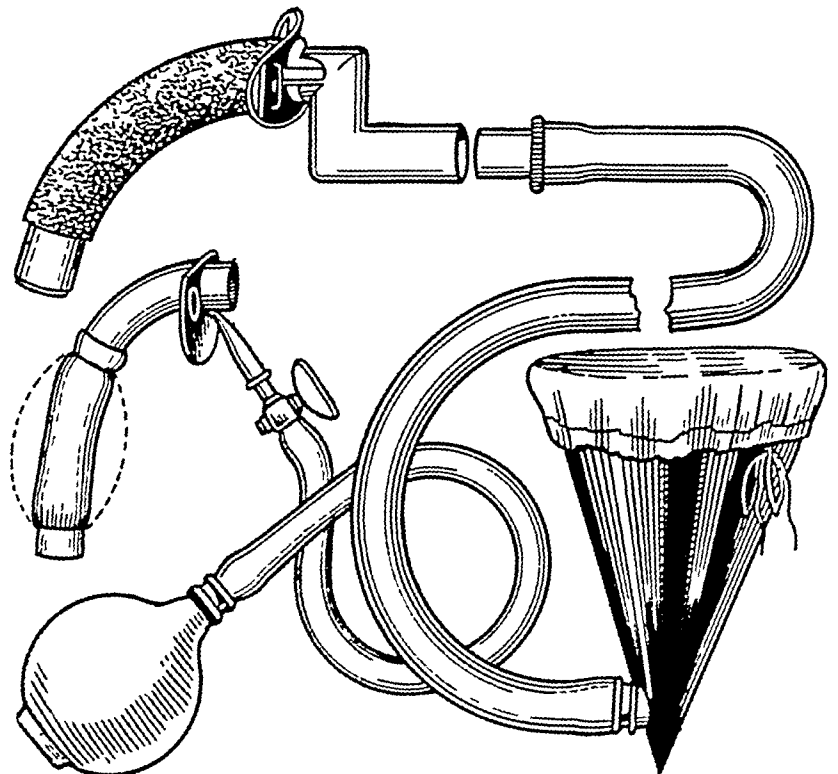
1866 ELLIS'S ALCOHOL AND ETHER INHALER. This inhaler was used for mixed anaesthetic vapours. Separate compartments were supplied for alcohol and ether in measured quantities. By revolving the inhaler on the angled socket, the proportion of mixture was controlled and indicated on the engraved scale.

1867 JUNKER'S CHLOROFORM INHALER. Hand bellows were the motive power in Junker's inhaler driving air through the chloroform. Later valves were incorporated to prevent liquid chloroform being directed to the patient.



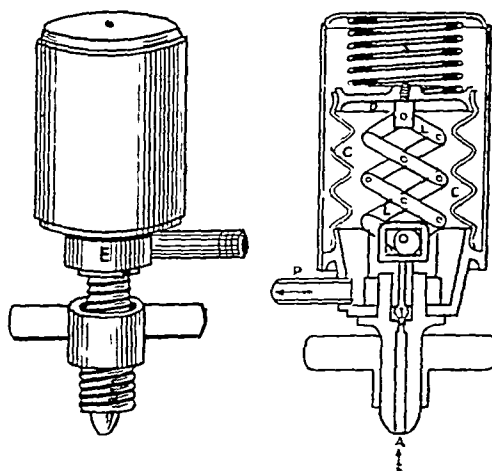
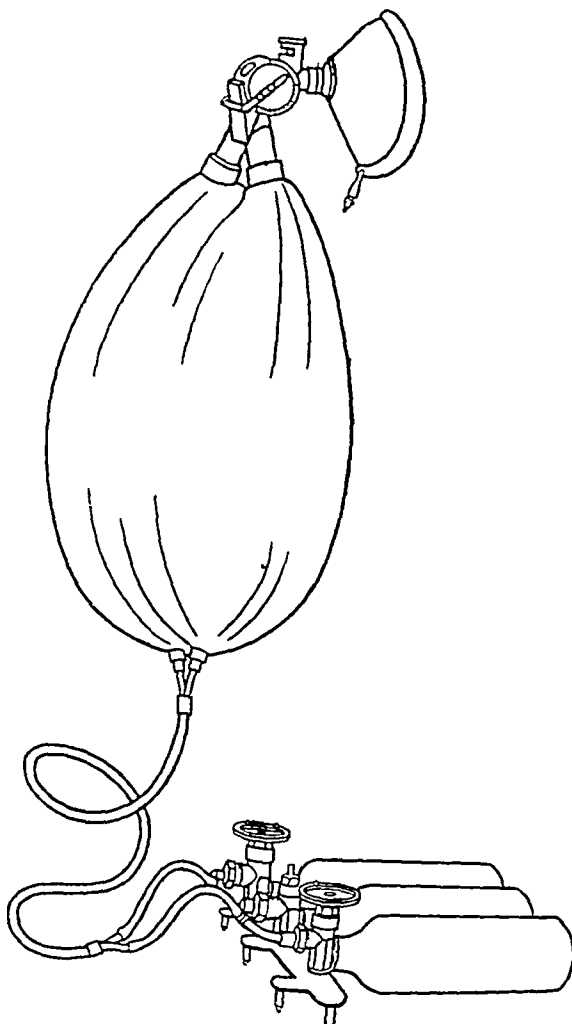
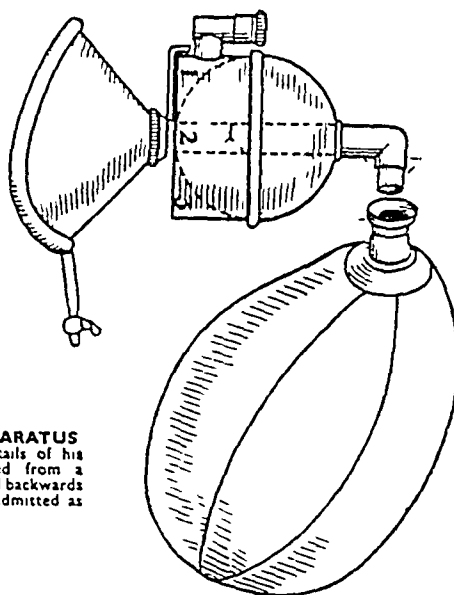
1867 COLTON'S NITROUS-OXIDE APPARATUS Nitrous oxide was usually prepared in the dental surgery by heating ammonium nitrate in a retort, passing the gas through a series of wash bottles to a gas holder

1871 TRENDLENBURG'S TRACHEAL APPARATUS Although Snow in 1858 had described a method of tracheal anaesthesia in animals, it was not until 1871 that Trendelenburg used this method in man. After preliminary tracheotomy he inserted a wide-bore tube with inflatable cuff and maintained anaesthesia by dropping chloroform on to a gauze-covered funnel attached to the tube



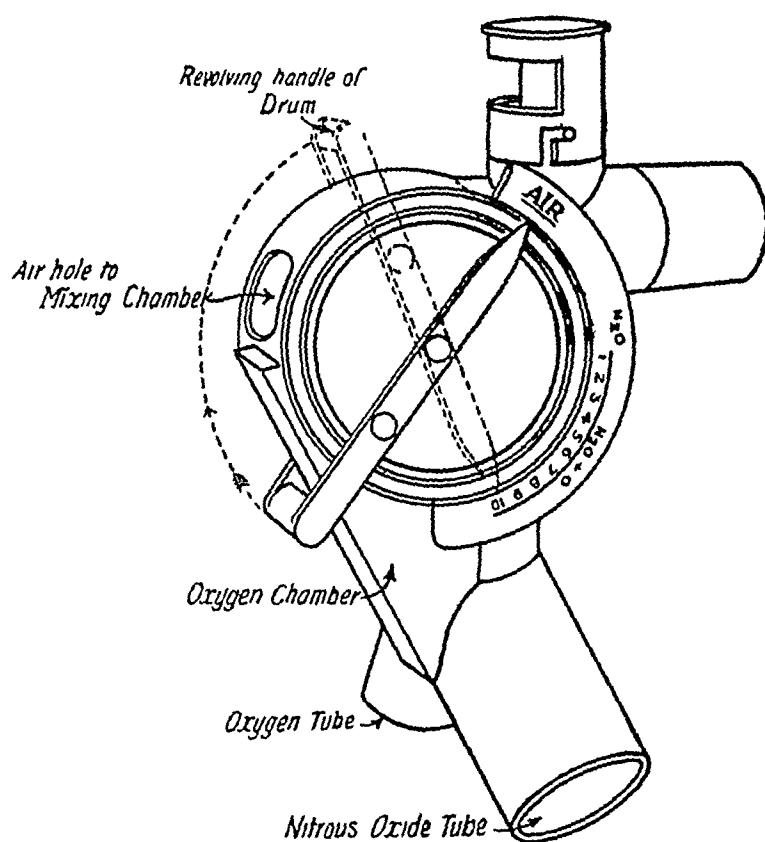
1877 CLOVER'S REGULATING ETHER INHALER This great forward stride in apparatus was the basis of many mechanical principles in use to-day. Many modifications followed, the most important being the enlargement of the inner bore suggested by Wilson Smith in 1908 and carried into practice by Hewitt in 1909, together with an improved drum control.

1876 CLOVER'S NITROUS-OXIDE AND-ETHER APPARATUS After 2,000 successful administrations Clover published details of his nitrous-oxide-and-ether apparatus. Nitrous oxide supplied from a cylinder whilst ether vapour came from a reservoir was breathed backwards and forwards from a bag attached to a facepiece. Air was admitted as required. [This apparatus is shown in BMB 827, Fig. 10.]

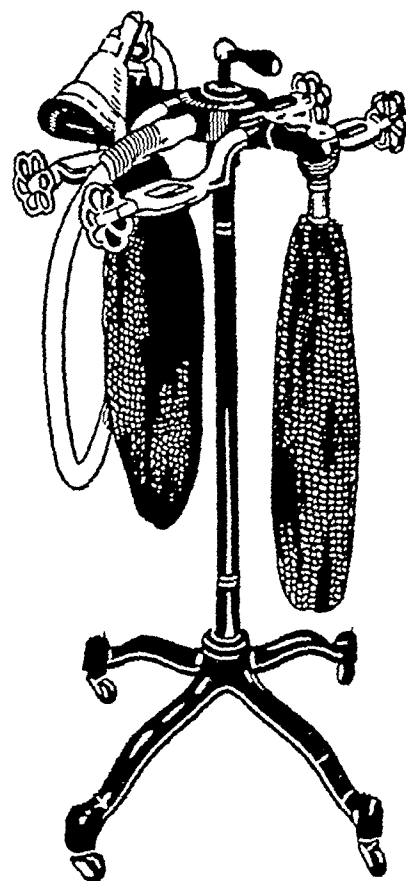


1882 BEARD'S PRESSURE-REDUCING VALVE To ensure a regular supply of gas as the cylinder pressure fell Beard patented his pressure-reducing valve. A bellows was lifted under pressure and in so doing drove down a screw thread into an orifice partially blocking it, thus reducing the rush of gas at high pressure.

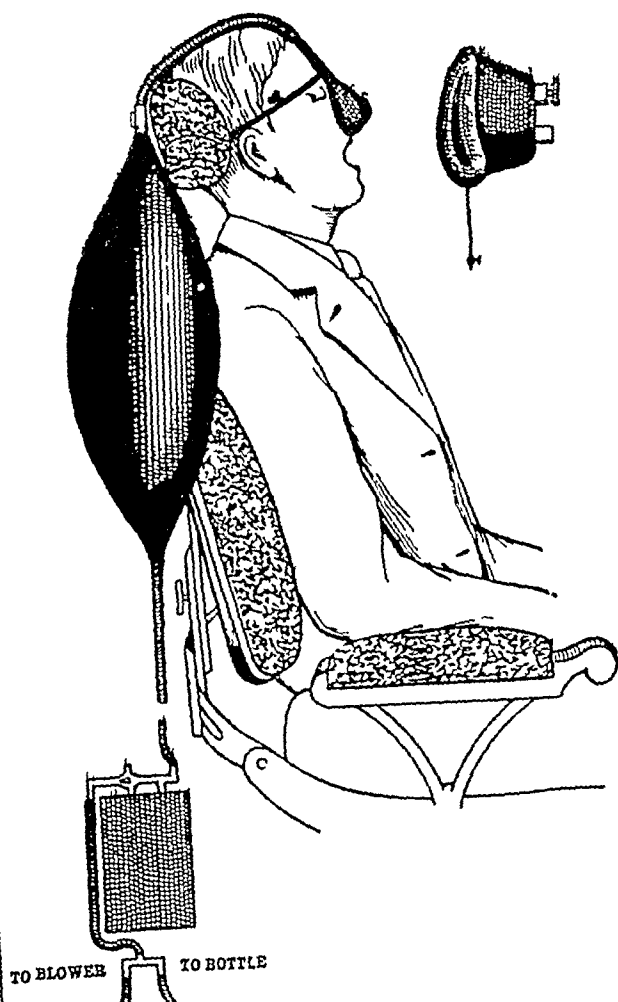
1892 HEWITT'S NITROUS-OXIDE AND-OXYGEN APPARATUS The first practical nitrous-oxide-and-oxygen apparatus of which the principle was to maintain by foot key control equal pressures of nitrous oxide and oxygen whilst hand manipulation of a regulating stopcock and mixing chamber governed the percentage of oxygen added to the nitrous oxide administered.



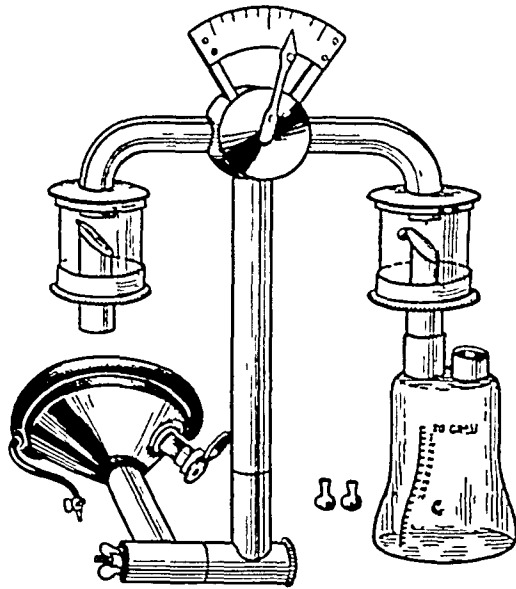
1892 HEWITT'S MIXTURE-REGULATING STOPCOCK. Observation of the pointer as it was moved over the scale marked on the side of the stopcock showed the percentage of oxygen being given



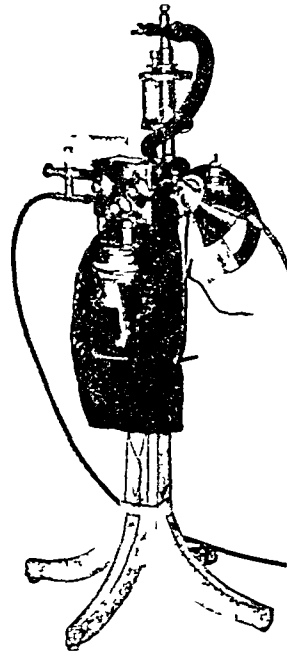
1899 CLARKE'S NITROUS-OXIDE-AND-OXYGEN APPARATUS. This is very similar to the S S White apparatus, which employed Hewitt's principle. Nitrous oxide and oxygen supply controlled by hand-valve adjustment with mixing chamber built into the casting



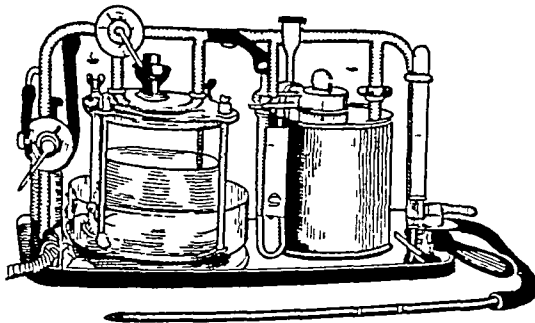
1898 COLEMAN'S NITROUS-OXIDE APPARATUS Coleman's apparatus utilized the suggestion by Hilliard that nasal inhalation should be used in dentistry



1903 VERNON HARCOURT'S CHLOROFORM REGULATING APPARATUS The designer claimed his inhaler not only regulated but accurately measured the strength of chloroform in air. Two indicating gravity beads floating at different levels enabled the operator to regulate the temperature to between 13° and 15° C. The stopcock was so made that when the pointer was at the end of the arc nearest the chloroform the maximum quantity being administered was 2%.



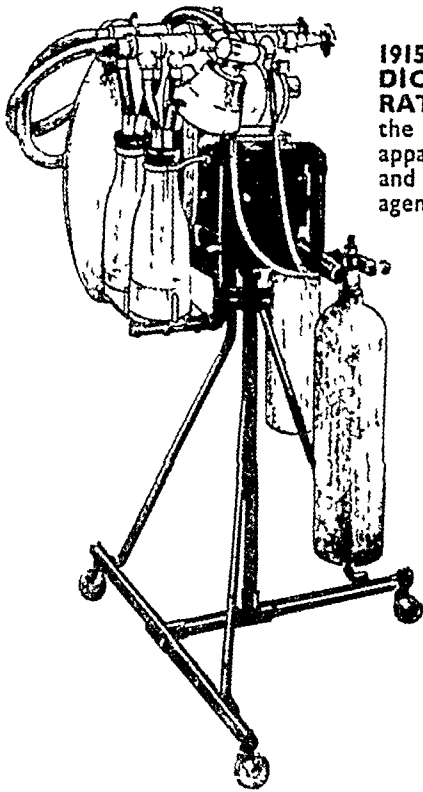
1910 McKESSON'S NITROUS-OXIDE-AND-OXYGEN APPARATUS McKesson produced the first truly intermittent gas apparatus nitrous oxide and oxygen only flowing as and when the patient inhaled and being automatically cut off during patient's exhalations.



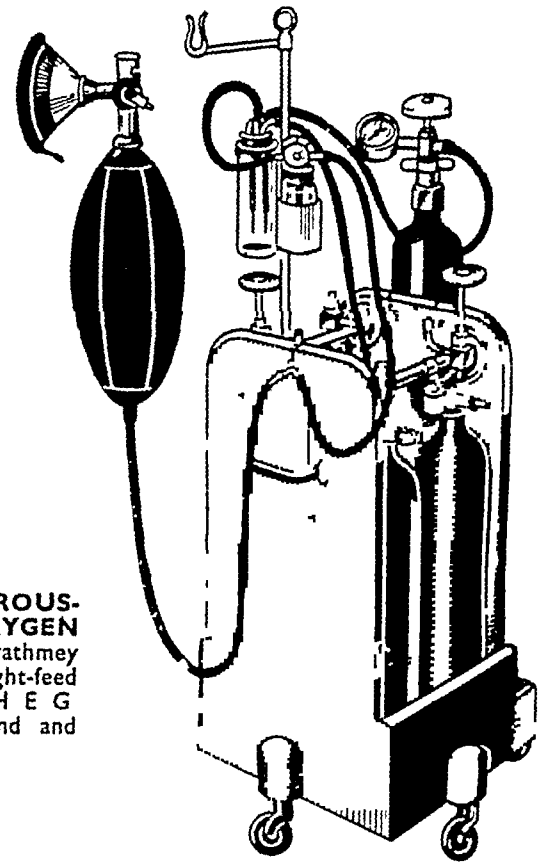
1912 KELLY'S INTRATRACHEAL APPARATUS Kelly claimed that warm moist air charged with definite proportions of ether vapour could be forced through a gum elastic catheter passed down to within an inch of the bifurcation of the bronchi.

1912 BOOTHBY AND COTTON'S WATER SIGHT-FEED FLOWMETER The original water sight feed though clumsy in design proved that the quantity of gas flowing to the patient could be measured by visual indication.

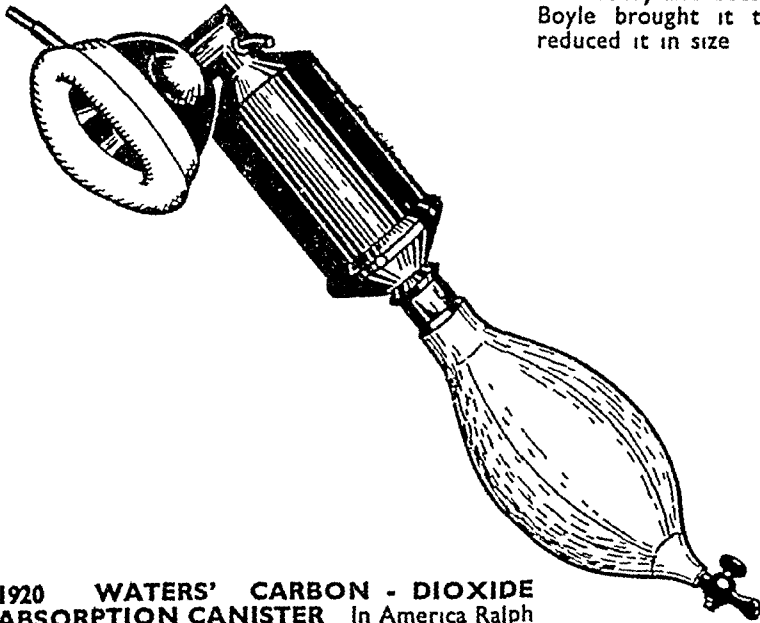




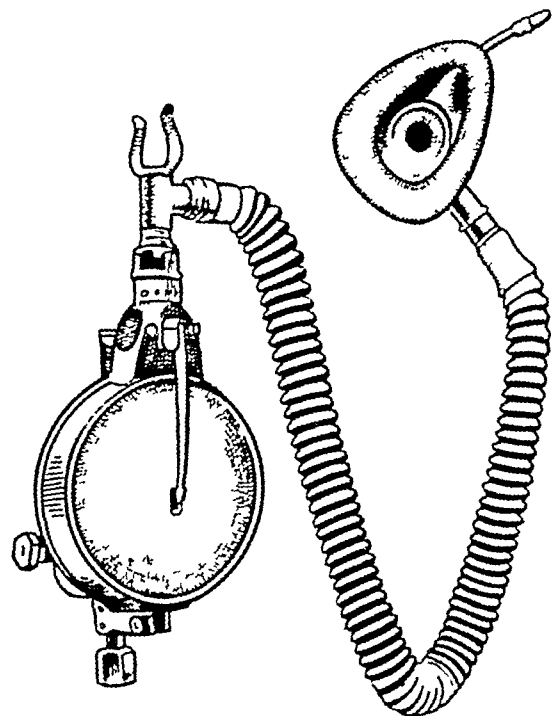
1915 JACKSON'S CARBON-DIOXIDE ABSORPTION APPARATUS. Dennis E Jackson made the first carbon-dioxide absorption apparatus, employing sodium hydrate and calcium hydrate as absorption agents and using an electric blower



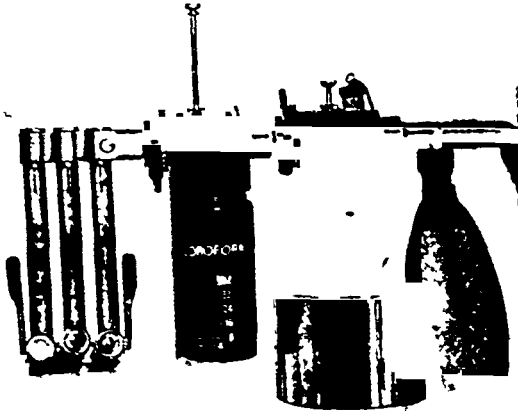
1917 BOYLE'S NITROUS-OXIDE - AND - OXYGEN APPARATUS After Gwathmey had improved the water sight-feed of Boothby and Cotton, Dr H E G Boyle brought it to England and reduced it in size



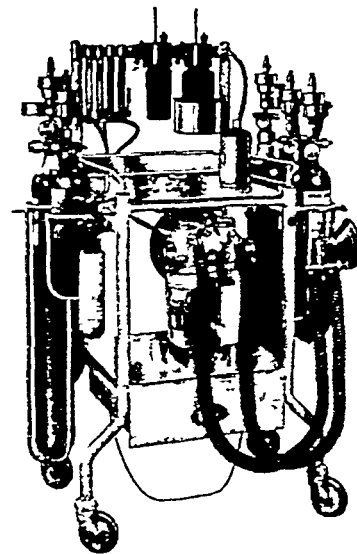
1920 WATERS' CARBON - DIOXIDE ABSORPTION CANISTER In America Ralph Waters had become interested in Dennis Jackson's experiments and after exhaustive research designed a metal canister to one end of which he attached a facepiece and the other a rebreathing bag



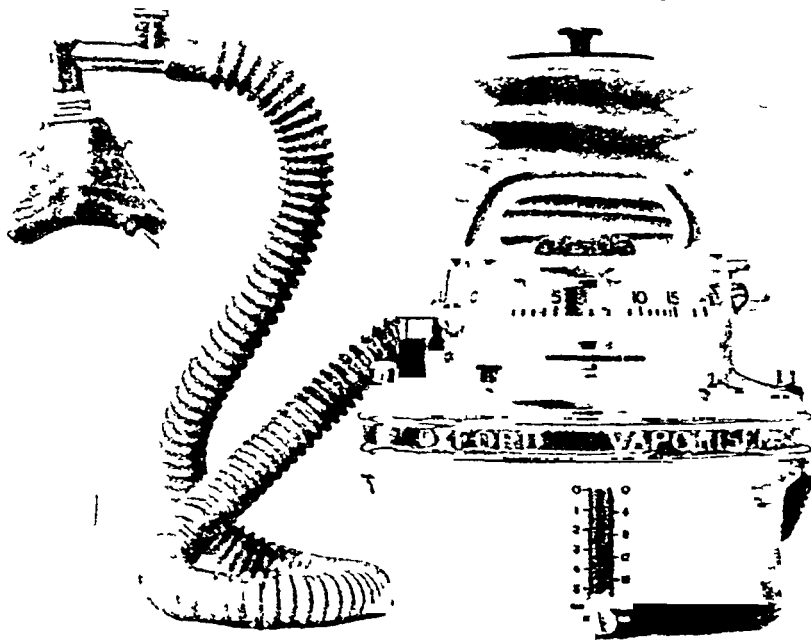
1933 MINNITT'S NITROUS-OXIDE-AND-AIR APPARATUS Dr R J Minnitt designed this apparatus in 1933 for the self-administration of nitrous oxide gas and air in midwifery. The apparatus is entirely automatic, gas and air at 55% flowing only as and when the patient inhales



1939 ROTAMETER BOYLE APPARATUS This consists of Rotameters with fine-adjustment controls for accurately measuring the flow of all anaesthetic gases combined with bottles for chloroform and ether



1941 COXETER-MUSHIN CARBON-DIOXIDE ABSORPTION APPARATUS The main features are minimal resistance two-way soda lime circuit wickless ether vaporizer rebreathing bag with lever for manually assisting respirations



1941 THE OXFORD VAPORIZER This apparatus was designed in the Nuffield department of anaesthetics Oxford. By the employment of hydrated calcium chloride as a chemical thermostat, the delivery of ether vapour at a constant temperature is assured. The proportion of inhaled ether vapour is directly determined by manipulation of the regulating tap

THREE INHALERS

DESCRIBED IN

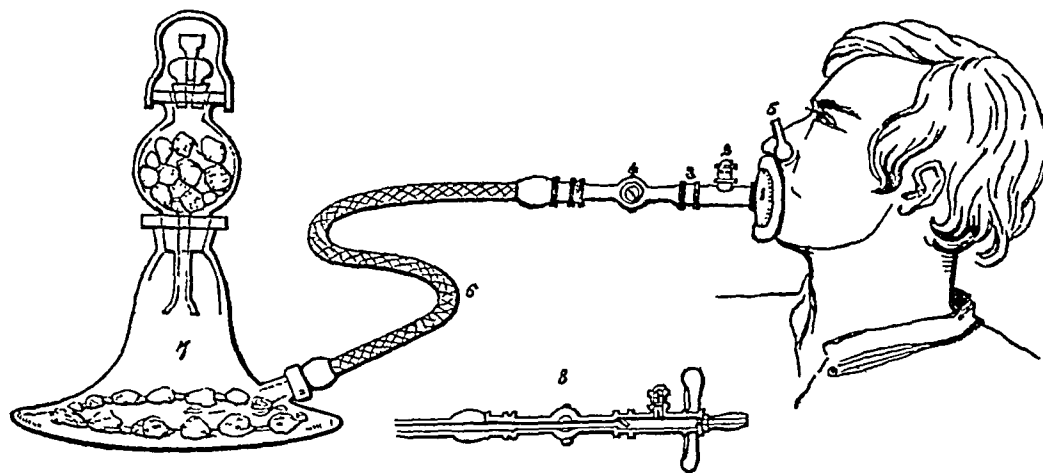


OF 1847

I HOOPER'S INHALER

This apparatus was employed by Mr Robinson, a dentist, who first used it on 19 December 1846. The following description is from the *Illustrated London News* of 9 January 1847.

"The apparatus employed consists of the lower part of Nooth's apparatus with a flexible tube, to which are attached a ball and socket valve and mouthpiece, similar to those commonly used for inhalation. The apparatus has been constructed by Mr Hooper, of 7, Pall Mall East, according to Dr Boott and Dr Robinson's instructions. It is very elegant in appearance.



"The apparatus has since been successfully used in operations at King's College Hospital, by Mr Fergusson, and, on Thursday last, by Mr Aston Key, at Guy's Hospital. Among other cases was the removal of an abscess from the great toe of a female. In this case the means was not entirely successful, for the patient screamed at the moment of the first incision of the instrument, but on recovery from the effects of the inhalation, was totally unconscious of the operation having been performed.

"The full effect of the vapour is produced in from one to two or three minutes generally, and, as soon as it is perceived, the operation is performed. If the stop-cock shuts off the vapour, and it is wished to let the patient breathe air, the nasal spring must be taken off. In prolonged operations this may be found desirable, and the inhalation of the ether may be renewed at

the will of the operator, the nasal spring, of course, then being placed on the nose."

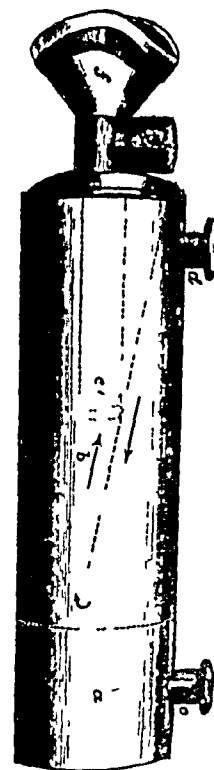
2 "SMEE'S HOT WATER ÆTHER INHALER"

A description in the *Illustrated London News* of 30 January 1847 of an inhaler devised by Mr Alfred Smee, Surgeon to the Bank of England.

"When this instrument is to be used the smaller chamber is filled with hot water (c), and a little æther, an ounce for instance, is placed in the larger compartment, which has sponge placed in it, to prevent its moving about. On inhalation, the current of air passes in the direction of the arrows, and is said to produce far more rapid effects than when any other instrument is employed.

"This instrument, with other ingenious arrangements for the Inhalation of æther, have been submitted to us, by the Proprietor of the celebrated Dépôt of Inventions, 201, Strand."

"Mr Smee's Inhaler, which is here figured, was made by Mr Ferguson, of Smithfield, and consists of a tin vessel, either circular or oval, about 8 inches long, and 3 wide, divided into two compartments—one smaller (A), to contain hot water, the other larger (B), to contain the æther. The large compartment is divided into two by a diaphragm and has another opening to admit the æther, and the entrance of the air (d). Into this larger compartment a tube is fixed, which has a valve at the extremity (e), for inspiration, and another valve (g) near the mouth-piece, for expiration. The mouth-piece (f) has an indian-rubber covering, to adapt itself to different mouths."



- 1 Pad for mouth, to be held by the operator
- 2 Horizontal valve for the escape of expired air
- 3 Vertical flap valve
- 4 Stop cock
- 5 Nasal spring
- 6 Elastic tube
- 7 Glass vessel, with a smaller one having pieces of sponge saturated with ether, and having a small perforated stopper, to be opened when the apparatus is in use
- 8 Sectional view of the pad, showing mouth-piece

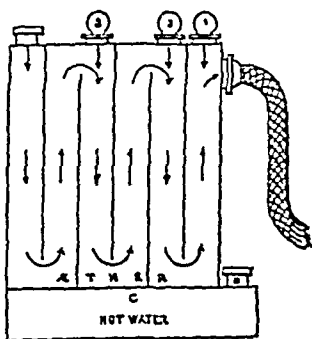
3 "THE GRADUATED DOSE INHALER"

The figure accompanies a letter from "Inhaler" to the *Illustrated London News* of 6 February 1847.

After describing personal experiments with advertised inhalers, he writes:

"The corollary to be drawn from these experiments, I again repeat, viz, that, in the administering of Ether, a *Graduated or Dose Inhaler* must be employed, by which the strength of the dose may, with facility, be adapted at any instant to the condition or temperament of the person to be operated upon, without the necessity of removing the tube from the mouth of the patient, and that the hot water apparatus, if not actually necessary in every case, is certainly useful to promote the activity and strength of the dose, when it may be required."

The inhaler is constructed in metal, and is divided into two chambers, the upper one to contain the Ether, and the lower one to contain warm water. The Ether chamber is divided by diaphragms into several cells the intention of these divisions is to cause the air, which enters at A, to perform the long route indicated by arrows, that it may be perfectly saturated with Ether before it leaves the Inhaler



The figures 1, 2, 3, on the top of the Inhaler, indicate several openings for the entrance of air, it is by these openings that the strength of the dose is graduated. For example, if No 1 is open, the air, entering at that point, will be in contact with only a small portion of the Ether vapour. No 2 being opened, will produce a stronger mixture, No 3, still stronger, &c, until, all being closed, with the exception of A, we then have the most powerful dose that can be had, without the assistance of heat.

In addition to this arrangement, a stop-cock is so constructed, and adapted to the tube, that the Ether can, at any time, be turned off, and the air turned on, or any proportion of each. This is a most valuable addition, since it gives the operator a perfect command over the power of the instrument, without in any degree, disturbing the patient.

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WONDERFUL EFFECTS OF ETHER IN A CASE OF SCOLDING WIFE.



MR PUNCH SUGGESTS THE
USE OF ETHER FOR THE
RELIEF OF A COMMON
AFFLICTION

This cartoon from *Punch* (1847) by John Leach famous comic artist reflects the popular interest in the ether discovery

Patient — "THIS IS REALLY QUITE DELIGHTFUL—A MOST BEAUTIFUL DREAM"

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WHO WAS THE FIRST SUBJECT OF ETHER ANAESTHESIA IN BRITAIN?

The following is an excerpt from a paper on "The patient a neglected factor in the history of medicine", by Dr Douglas Guthrie (*Proc roy Soc Med*, 1945, 38, 490-494)

"The news of ether soon reached England and Robert Liston was the first to try it at University College Hospital in December, 1846. The patient's name was Frederick Churchill, a butler aged 50, and he had a malignant growth of the leg, which demanded amputation through the thigh. Peter Squire administered the anaesthetic, and Liston completed the operation in thirty-two seconds. When the patient recovered consciousness he did not know the operation was over, but on seeing the uplifted stump he burst into tears. The scene in the theatre was most impressive and tense. But was the patient the first subject of ether anaesthesia in Britain? Apparently not, according to Sir Charles Brown, of Preston, who was a spectator of Liston's amputation and who describes it in *Sixty-four years a doctor* (1922). 'Before the patient was brought in,' he wrote, 'the anaesthetist asked the students for some volunteer who would submit to be anaesthetized. A young man named Shelbrake, of powerful build and a good boxer, at once came forward and lay on the table. After he had inhaled ether for half a minute he suddenly sprang up, felled the anaesthetist at a blow and scattered the students before him like sheep before a dog. He soon regained his senses and then the patient was brought in.'"

[The date of Liston's first operation with ether was 21 December. Dr Francis Boott, in a letter dated 21 December, 1846 and published in the *Lancet* of 2 January, 1847 (p. 8), describes the extraction of a molar tooth under ether narcosis on 19 December, 1846. The patient was a Miss Lonsdale and the dentist a Mr Robinson. The operation took place in the study of Dr Boott, who had received news of the ether discovery in a personal letter from Bigelow, of Boston. It seems clear, therefore, that Miss Lonsdale was the first subject of ether anaesthesia in Britain.—Ed.]

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THE FIRST USE OF CHLOROFORM IN SURGERY

The story of the discovery of the anaesthetic properties of chloroform has often been told, but the circumstances of its introduction into surgical practice are not so generally known, and may be worth repeating.

A few days after the famous experiment at 22, Queen Street, Edinburgh, when, on the evening of 4 November 1847, Sir James Young Simpson (then Dr Simpson) and his two assistants, Drs Keith and Matthews Duncan, found themselves prostrate beneath the dining-room table in the grip of a drug "far better and stronger than ether," Simpson called at the Royal Infirmary, where he hoped that there might be an opportunity of testing the effect of chloroform in surgery. As he writes in his "Account of a new anaesthetic agent," he met Professor Miller, the professor of surgery, who happened to have several patients awaiting operation. "The first was a Highland boy, four or five years old, affected with necrosis of the radius. He knew no language but Gaelic, and it was therefore impossible to explain to him what he was required to do. When a handkerchief, on which some chloroform had been sprinkled, was held to his face, he became frightened and struggled. He was held gently, however, by Dr Simpson, and obliged to inhale. After a few inspirations he ceased to cry or move, and fell into a sound snoring sleep. A deep incision was now made down to the diseased bone, and, by the use of the forceps, nearly the whole of the radius, in the state of sequestrum, was extracted. During this operation, not the slightest evidence of the suffering of pain was given. He slept on soundly and was carried back to the ward. Half an hour afterwards he awoke with a clear merry eye and placid expression of countenance, wholly unlike what

is found after ordinary etherization. On being questioned by a Gaelic interpreter who was found among the students, he stated that he had never felt any pain and that he felt none now." Two other patients were submitted to operation under chloroform, and we are told that for the three cases "the whole quantity of chloroform did not exceed half an ounce." "From that day to this," wrote Professor Miller in his paper on chloroform published in the following year, "I have never ceased to employ chloroform. It is by far the best anaesthetic agent as yet known."

Douglas Guthrie

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DAVID WALDIE, A FORGOTTEN PIONEER OF CHLOROFORM ANAESTHESIA

Although Sir James Young Simpson, the distinguished Edinburgh obstetrician, is rightly acclaimed as the discoverer of the anaesthetic properties of chloroform, he was assisted towards the discovery by one whose name is seldom mentioned by writers on the subject, but who nevertheless deserves to be remembered for having suggested to Simpson that chloroform might be worthy of a trial in his experiments. In his original paper on the "New anaesthetic agent", Simpson acknowledges his indebtedness to Mr David Waldie, of Liverpool.

Waldie was a medical man, holding the diploma of the Royal College of Surgeons of Edinburgh. For a time he practised in his native town of Linlithgow, but as he was more interested in chemistry than in clinical medicine he accepted an appointment with the Liverpool Apothecaries Company. In company with his partner, Mr John Abraham, he conducted some experiments, and although he gives no details of his observations in his paper on chloroform which he gave at a meeting of the Liverpool Literary and Philosophical Society on 29 November, 1847, there is no doubt that he was aware of the properties of the drug when, in the course of a visit to Scotland during the previous month, he recommended it to Dr Simpson, then in search of an anaesthetic without the disadvantages of ether.

Of course, Waldie never claimed to have discovered the anaesthetic properties of chloroform, and no one alleges that he did so. What he did was to recommend chloroform to Simpson for his experiments, thus forging a most important link in the chain of events which led to the discovery. Waldie afterwards went to India as a chemist, and he died at Calcutta in 1889. He holds a worthy place among pioneers of anaesthesia, and it is fitting to recall his service to humanity.

Douglas Guthrie

835

DR MATTHEWS DUNCAN'S EARLY TRIAL OF CHLOROFORM

The following is an excerpt from the diary (25 July 1870) of Sir Robert Christison, the great Edinburgh toxicologist. It is taken from *The life of Sir Robert Christison, Bart* (Edinburgh, 1886, Vol. II, pp. 352-353).

"On asking Dr Matthews Duncan to repeat a remarkable statement he made to me a few months ago, relative to his concern with the discovery of the anaesthetic virtues of chloroform, he gave it me thus. One day, when Sir James Simpson and he were in Dr Gregory's laboratory at the College, he (Dr Duncan) got possession of every liquid in the laboratory which he imagined 'would breathe'. Four or five bottles were thus carried off, and chloroform was one. At this time, the correspondence with Mr Waldie about anaesthetics, and the suggestion by that gentleman to try chloroform, had not been heard of by Dr Duncan. One forenoon Dr Duncan made trial of the chloroform. He had previously experimented on himself with various substances, but found none suitable. On trying chloroform, he was convinced that the article sought for was found. The same or next evening the trial was repeated by Dr Keith, Sir James, and himself. This was the trial which is now a matter of history, but the previous trial has never been noticed."

THE FIRST SPECIALIST-ANAESTHETIST

John Snow, the first physician to make a speciality of the administration of anaesthetics, was born at York, 15 June 1813. The eldest of several boys, he was educated privately in the town before leaving at the age of 14 for Newcastle, where he was apprenticed according to the custom of the time to a surgeon. Here, in 1831-32, Snow laid the foundations of the work on cholera that has tended to overshadow his fame as a pioneer anaesthetist. But in 1833 he left Newcastle and eventually reached London in 1836. He gained his M.R.C.S. in 1838 and his M.D. London in 1844 while he was also admitted a licentiate of the Royal College of Physicians. As he had carried out some experiments on respiration and asphyxia, he was well qualified to investigate the use of sulphuric ether as an anaesthetic when news reached England in 1846 that it had been tried in America.

Believing that greater success would attend the use of ether in this way if the mode of administration were improved, Snow made his own investigations until he had become proficient, and it is appropriate that his name should be perpetuated by his inhaler. The success of a druggist of his acquaintance in an ether practice¹ encouraged Snow to present himself at St George's Hospital, where he obtained permission to administer ether to outpatients who attended for tooth-drawing. Snow's work so impressed a certain Dr Fuller that he was instrumental in arranging that Snow should act as anaesthetist at surgical operations, and as he also developed a large private practice he quickly became established.

He records that he gave ether in 152 cases before the introduction of chloroform, but in only twelve cases afterwards. It is interesting to note however, that 'nearly all the great operations of surgery [that were performed at that time] were included several times amongst the cases' in which ether was given. Thirty three were amputations of the thigh, leg or arm with a mortality of 24%. Age was no bar for Snow often administered ether to infants and the aged. Few pioneers can have documented their work better than Snow, for he not only kept a record of his cases in diary form but notes of his experiments. He also had his Boswell in Sir Benjamin Ward Richardson, who published Snow's work on chloroform¹ after the author's death, and was responsible for the preservation of most of the known facts concerning Snow's life.

Snow used ether only once in an obstetric case, but when Sir James Young Simpson introduced chloroform for this purpose Snow quickly realized its value. He administered chloroform to H.M. Queen Victoria on 7 April 1853 at the birth of the Prince Leopold. On this occasion the chloroform was given on a handkerchief in 15-minum doses, but Snow states:

I nearly always employ in obstetric cases the inhaler that I use in surgical operations. I find the inhaler much more convenient of application than a handkerchief, and it contains a supply of chloroform which lasts for some time, thereby saving the trouble of constantly pouring out more. This inhaler with a small bottle for the chloroform was preserved in its original wooden case by Sir Benjamin Ward Richardson. On 14 April 1857 Snow administered chloroform at the birth of the Princess Beatrice.

In these days when plastic surgery is a topic of current interest it is worth noting that Snow administered chloroform in fifty cases arising from injury or disease. It was his opinion that the greater number could not have been performed before the discovery of narcotism. It is also worth while noting that twenty-four of his cases were connected with deformities caused by burns.

Perhaps the queerest case in which Snow was called upon to administer chloroform is best described in his own words:

"In June 1852 I gave chloroform to a girl, five years old and Mr Fergusson [Sir William Fergusson (1808-77)] scooped out some polypus growth from the right nostril and also an oval softened body, rather bigger than a horse-bean, which was a young orange that the child had pushed up her nose in India."

Snow died at the height of his career on 16 June 1858.

F. Tubbs

¹ Snow J (1858) *On chloroform and other anaesthetics their action and administration*. Edited with a memoir of the author by Benjamin W. Richardson. London.

POPULAR REACTIONS TO THE ETHER DISCOVERY

Examination of reports on the discovery which appeared in the newspapers and periodicals of the day leave one with the impression that the public were somewhat cold blooded on the subject, they were interested in the discovery as a novelty rather than as a means to relieve human suffering. Painless surgery should have had a more personal appeal than advances in any other branch of medical science, the average man would be less interested in the sterilization of the surgeon's instruments, for instance, than in the knowledge that he would not feel the cut of the knife.

In the *Athenaeum* of 2 January 1847, the discovery was discussed with reserve and a certain amount of scepticism.

"Animal Magnetism, it appears, is likely to meet with a powerful opponent." *A priori*, there seems no reason why a man should not be made dead drunk—for such appears to be the state of the individual under the influence of the vapour of ether—for some minutes by some of the volatile narcotics which are used in medicine. There is nothing here of that hocus pocussing which characterizes the practices of the mesmeriser. At the same time we do not regard the proof of unconsciousness as perfectly satisfactory in these ether cases. In fact, we have too vivid a recollection of the tricks of magnetical impostors not to be on our guard against the possibility of shamming, even with ether.

A more enthusiastic report was contained in a letter dated from Boston, USA, on 29 November 1846, and in this the writer tells of the great news which had greeted him on his arrival from England. He mentions having been told by an eminent American surgeon that the discovery was likely to prove most useful in large operations of a painful character, rather than in those requiring delicate treatment.

First Use in England

One of the first medical men in England to hear of the recent happenings in America was Dr Boott, to whom Dr Bigelow of Boston had written on the matter. Despite Morton's rather stupid attempts to keep secret the ingredients of the agent used in his expositions, and to which he had given the name "Letheon," it was easily identifiable, by its odour alone, as pure sulphuric ether. Dr Bigelow lost no time in communicating this to his friends, including Dr Boott, who, in turn, sent word to a dentist friend of his named Robinson. The latter was a "live wire" and on hearing the news was round "in a jiffy" and ready for the "first fling." He spent the remainder of that day (17 December) and the following in rigging up an apparatus from a "Nooth's inhaler" to which he fitted a flexible tube and mouthpiece. On the morning of the 19th, in the presence of Dr Boott and his family, he put a lady patient to sleep and extracted a molar tooth with complete success.

Liston's First Amputation under Ether

Sir Benjamin Ward Richardson in an article on 'The mastery of pain' which appeared in *Longman's Magazine* in 1892, quotes a description which Sir John Forbes gave him of Liston's first amputation under ether at University College Hospital. Liston who had cultivated extreme speed in operating, removed the limb within the minute. "Everybody seemed pale and silent except Liston, who was flushed, and so breathless that when he broke the silence with the word 'Gentlemen' he almost choked in its utterance."

Distinguished Audiences

Many of the early operations by the new method were attended by a concourse of distinguished spectators. The name of Prince Louis Napoleon Bonaparte figures in a number of newspaper accounts and he was one of the first to ask Robinson (the dentist already referred to) to allow him to witness a demonstration which he watched with almost childish wonder 'as if he were under a fascination'.

This practice of admitting members of the public was sometimes an embarrassment. The *Times* of 15 January 1847 mentions that a large number of celebrities including Jerome Bonaparte were at St George's Hospital on the previous day when operations were performed. The first case was a failure.

the patient having to be removed without the operation being started. The second patient had an uncomfortable time for ten minutes, "turning very red, or rather purple," and in such a state of anguish that the onlookers commented that the effects were worse than the operation. Eventually the surgeon judged the patient to be ready and proceeded to remove the finger, whereon the poor fellow shouted loudly and snatched his hand away! The third case fortunately gave no trouble, and a successful amputation was performed.

"The quicker the surgeon, the greater the surgeon"

Richardson, in the article referred to above, describes the horror of operating day when, as he puts it, "the quicker the surgeon, the greater the surgeon" was the order of the day. He mentions one operation performed by Prof. Lawrie, and carried out with such dexterity that it was over before the patient uttered a single cry, though the poor wretch screamed and struggled throughout the closing stages of the nerve-shattering business. Richardson and his fellow students were almost overcome, the new methods were at least appreciated by men who had gone through such experiences.

Some Disparagements

It seems almost inconceivable that the introduction of painless surgery should have been subjected to adverse criticism. Nevertheless it was argued that the day of the great surgeon was over, that squeamishness over infliction of pain could not go hand in hand with bold, dexterous operating. It was further suggested that to banish pain was contrary to the laws of nature, that pain was necessary to indicate injury, the seat of injury, and the cause of injury.

A more sinister objection was made on the grounds that it provided a dangerous weapon for the evil-doer. Some saw in it an affront to divine law, man was born to suffer, and anaesthesia was, in effect, an attempt to cheat that law and could end only in disaster. Finally, it was foretold that as the practice became more general, the number of deaths under anaesthesia would prove too heavy to be endured. This last view was fairly widespread, and after a few isolated cases had ended fatally, it seemed as though ether anaesthetization was doomed.

The *Times* of 19 March 1847 devoted nearly two columns to the report of an inquest on a young woman who had died a few days after an operation under ether. In this case a verdict to the effect that the woman died as the result of the administration of ether was brought in, and accepted by the coroner and the surgeon concerned. The prominence given to this case, with ether as the "villain of the piece", in contrast to the brief paragraphs devoted to successful operations, augured ill for those who were striving to win public confidence in the new method.

In his work *On etherization in surgery and practical medicine*, 1847, Sir John Forbes gave an amusing example of the slender grounds on which etherization was condemned. A man was said to have died of bleeding from the lungs in Guy's Hospital after taking ether during an operation for hernia. On inquiry at the hospital, the man was found to be still alive, and on being questioned as to the bleeding from his lungs, he stated that the day after the operation "he had pricked his gums while picking his teeth with a pin—and it was the product of this operation, not of the ether, seen in the spitting-pot by the patient's bedside, that was bruited about town as of itself sufficient to settle the question of etherization in all future time."

Ether outmoded by Simpson's use of Chloroform

As a "discovery" ether was short-lived. To the public, with their love of the "latest thing", Simpson's use of chloroform, and the paper on the subject which he read on 10 November, 1847, seemed to outmode ether. To the man in the street it was something newer, and consequently superior, the word "chloroform" came into use as a verb in place of anaesthetize, and ether was forgotten.

Experiments on Plants

Scientists were not slow to try out the effects of ether in other directions. The *Athenaeum* of 26 June, 1847, describes an experiment carried out by M. Clemens, Professor of Natural Sciences at the College of Vevay. The Professor placed a

branch of the common barberry under a drinking glass with a small quantity of ether, and found on withdrawing it, and touching the stamina at their base, that they had lost all their irritability.

Early use in Veterinary Practice

The *Times* of 29 January 1847 reports the successful operation under ether on a horse at the Royal Veterinary College, whilst a novel use is mentioned in the *Athenaeum* for 14 August, 1847.

"Etherization of Bees—Several successful experiments have, it is said, been recently made in France on the etherization of bees—so as to be able to take their honey while they are in a state of inaction without the necessity of destroying their hives."

On the 4th September appeared the following:

"Acting on the hint recently dropped in this paper from the experiments of a French naturalist, a gentleman of Great Marylebone Street has contrived an apparatus for etherizing bees, which does its work without the least trouble. The bees are at first much agitated, then stupefied, and fall to the ground—when they may be handled with impunity. The effect is produced in little more than a minute and a-half."

T. H. Bishop

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**THE BEGINNINGS OF SURGICAL ANAESTHESIA
IN FRANCE ETHER AND CHLOROFORM¹**

ANDRE HAHN, M.D.

Chief Librarian, Faculty of Medicine, Paris

It was the beginning of the year 1847. Ether anaesthesia had made its début in major surgery in the United States nearly three months before, on 16 October, 1846. In London, on 21 December, Liston, in his turn, had just performed his first successful operation under anaesthesia, and in France, Jobert, assisted by an American surgeon, had made his first successful attempt at etherization on 24 December at the Hôpital St-Louis. The fame of Jackson and Morton had crossed the Atlantic and aroused in Europe a lively curiosity, tempered by a certain reserve in the absence of substantial experimental evidence.

On 12 January, 1847, Professor Malgaigne drew the attention of his colleagues at the Académie de Médecine to "a property of ether not previously known, or, if the property itself was known", to "a new application" of it, and recalled communications in English and American journals on the fact that "the respiration and inhalation of ether deadened general sensibility to such an extent that surgical operations performed on patients in this state caused little or no pain."

This was the first official intimation of the discovery which promised so much for the future. Moreover, Professor Malgaigne reported five cases to the Académie in support of his statement. In the experiments carried out in his department at the Hôpital St-Louis, he employed a tube containing a certain amount of ether. The tube was inserted into one nostril while the other was occluded, the mouth being kept closed during inspiration and open during expiration.

Professor Velpeau was present at this meeting, it was he, it was remembered, who had, in 1839, written the following lines in his *Nouveaux éléments de médecine opératoire* [second edition]: "The avoidance of pain, in surgery, is a dream one can no longer pursue to-day", and who had not thought it right to experiment as yet with the secret method which Morton had already communicated to him, as he was afraid of injuring his patients, and

[¹ Translated from the French by A. H. S.]

was still doubtful about the dangers of sustained inspiration of ether. However, when confronted with the results of Professor Malgaigne's tests, he recognized that the dream was likely to become a reality.

Velpeau was able to define his position a few days later, at a meeting of the Académie des Sciences held on 18 January 1847. The question of priority in the invention of the practical application of the soporific properties of ether was to give rise to much controversy in France. Already, Ducros, at the beginning of the year, was claiming priority in view of experiments made public as early as 1842, and of his work of March, 1846, on the physiological effects of sulphuric ether. On this occasion, the secretary of the Académie, M. Elie Beaumont, asked the meeting to proceed to the opening of a sealed envelope deposited by him at the session of 28 December 1846, this contained two letters from Jackson, the first dated 13 November 1846, in which he described his work, his connection with a dentist (he does not quote Morton's name), and the first operations under anaesthesia performed at the Massachusetts General Hospital and asked the Académie to appoint a committee to make the necessary experiments to confirm the truth of his statements. In the second letter, dated 1 December, he confirmed the success of operations performed under the application of ether vapour.

Professor Velpeau then declared that the secret in question was no longer a secret, since the press had divulged it as early as November, and as it was more than a month since Dr. Warren of Boston, had informed him of it and since Dr. W. Fisher, of the same town, had, about the middle of December, proposed that a trial should be carried out at the Charité. He went on to recall the experiments of Jackson and Morton, the trials carried out in London, and those performed in Paris by the doctors Roux at the Hôtel-Dieu, and by Laugier at Beaujon, the results of which were no more conclusive than his own at the Charité, while acknowledging the value of those of Professor Malgaigne, which had been more successful. He emphasized the uncertainty and inconstancy which had been observed both abroad and in France, and the short duration of the effects, which lasted no longer than 2-5 minutes. He added that this inconstancy might be due 'as much to the imperfections of the apparatus employed as to the actual nature of the drug or the diversity of individual constitutions'.

The Académie des Sciences, then, seemed to show a certain degree of reserve. Velpeau wanted a multiplication of trials, Serres wondered if this artificial killing of pain had not more untoward effects than pain itself. Professor Roux thought that this new method could probably not be applied indiscriminately in all circumstances, and suggested that, until further information was available, the subject in question 'should remain enclosed within the circle of scientific communications and publications'. The scope of the new method was, however, to be quickly appreciated and disclosed in innumerable papers read to the learned societies, in Paris and in the provinces. On 25 January 1847, Charnière submitted his new apparatus for inhaling, which had already been put into use in most of the Paris hospitals to the Académie. Professor Gerdy had made use of this on 21 January for a trial of the effects of ether on himself. All France was acclaiming the discovery. Sédillot at Strasbourg, Simonin at Nancy, Bonnet and Bouchacour at Lyons, Bouisson at Montpellier, and J. Roux at Toulon, were experimenting on improvements in apparatus. New etherizers were constructed by Luër, Magouti, A. Bonnet, Ferrand, Porta (of Pavia) and J. Roux.

At the Académie des Sciences meeting of 1 February, 1847, it was Velpeau's turn to admit, in a brilliant speech, what great promise this subject held for the future, and what unforeseen importance ether anaesthesia would assume when the flaccidity of the muscular system became generalized. 'On all sides', he concluded, 'the facts, confirmed by one another, are becoming immensely interesting'. But he was to find an implacable antagonist in Magendie. The famous physiologist rose up in wrath against this 'recital of the marvellous effects of sulphuric ether upon which the press has seized to satisfy the insatiable, avid craving of the public for the miraculous and impossible. It is not enough to desire good', he cried, 'one must also take steps to guard against the evil' that the drunkenness caused by ether might produce in the hands of unskilled, ignorant men, or even in the intimacy of the family circle.

Velpeau's reply was more than a defence. It marked the date of the final acceptance in France of the discovery of Jackson and Morton.¹ The essential result, and the point of greatest importance to surgery, according to the eminent teacher, was the insensibility produced in patients submitted to the influence of ether. This was now a fact established by observation, and the result was practically constant if the procedure was carefully carried out. There was, however, another point of secondary and varying significance, namely, the restlessness produced by pleasant sensations or dreams, or by distressing ideas, and shouts or remarks which might cause inconvenience in surgical operations. This fact was certainly undeniable, but 'who knows but that we may learn in the near future how to control or avoid these disordered movements, and what is to prevent us subjecting a person to the action of ether just far enough to find out how he is affected, before proceeding to the final induction', as indeed Velpeau himself had done in a number of cases.

It remained to find out whether patients thus treated ran any danger. Velpeau affirmed that 'absolutely nothing had happened to them, up to that time, which justified the indictment of ether by reason of the very shortness of the period of insensibility (2 to 5 minutes), and of the fact that the patient recovered in 2 or 3 minutes, without any sign of suffering and without any apparent disturbance of the system'.

Through Velpeau, then, etherization achieved a position of honoured acceptance in France, and its fame was so great that, like Ducros and Wells, Jackson, and then Morton, strove for recognition of their claims to priority of invention. A lively controversy arose when the Académie decided to award the Monthyon prize for the years 1847-48 to the inventor of anaesthesia, and, eliminating Wells, to divide it between Jackson and Morton, as being 'indispensable to one another'. This prize was founded in 1819 as a reward for those who had earned, by some act or piece of work, the title of 'benefactors of humanity'. The hostility between the two former collaborators was now manifested as acutely as it had been earlier in America.

Velpeau in his speech, had drawn the attention of the Académie to the two chief uses of ether anaesthesia: the killing of pain and the paralysis of muscular action. He had hinted at its possible advantages in obstetrics. On 23 February 1847, Professor Dubois informed the Académie of its application in labour, and announced the first instance of its use in this connection by Professor Simpson on 17 January 1847, at Edinburgh. Fournier-Deschamps had also used it in France, on 30 January, for a forceps delivery.

The physiologists had likewise attacked the physiological and psychological aspects of the problem. Flourens pointed out the action of ether on the cerebral lobes and cerebellum. Longuet observed the progressive invasion of the nervous centres. These investigators, however, were anxious to experiment with other substances possessing analogous properties.

It was at this time, when ether had barely made its conquest of France, that, on 8 March 1847, at the Académie des Sciences, Flourens, in connection with a *Note touchant l'action de l'éther sur les centres nerveux*, pointed out that he had obtained the same results with 'l'éther chlorhydrique' as with sulphuric ether. He stated, moreover, that 'l'éther chlorhydrique' had led him to try a new substance known as chloroform, which produced total 'etherization' in a few minutes.

Chloroform had been discovered in 1831 by Soubeiran in the course of distilling alcohol with calcium chloride, studied by Liebig (1832) and chemically defined and classified by Dumas (1835), but was still little known in France at the time when its practical application was made known by Simpson's paper (10 November 1847). Simpson, who had, after personal experiments, been using the new agent for some time in Edinburgh to produce insensibility in surgical and obstetrical practice, represented chloroform as possessing all the advantages of sulphuric ether without the chief disadvantages: a smaller quantity of the anaesthetic was necessary, it had a quicker and more complete effect, the process of inhalation was pleasanter, the cost lower, the smell was less unpleasant and did not permeate the patient. It was easy to transport and no inhaler was necessary. Simpson supported his statement with a description of two operations performed at the Edinburgh Royal Infirmary by Professor Miller.

¹ [Dr. Hahn's references to Jackson indicate that he is still given more credit by European writers than would be the case in Britain and the USA.—Ed.]

in the presence of Professors Dumas and Milne Edwards of Paris, Dr Christison and Sir George Ballingall. This new therapeutic agent was soon to be tried out all over France, and its success was such that ether anaesthesia was practically abandoned in current practice.

The vogue of chloroform was, however, rapidly eclipsed by a series of grave failures, the possibility of which Flourens had foreshadowed in his prophetic statement: "If sulphuric ether is both wonderful and terrible, then chloroform is still more wonderful and still more terrible."

The battle between ether and chloroform had begun, it has continued to the present day to split the masters of surgery into two camps.

The Paris school declared itself resolutely in favour of the use of chloroform. The Académie de Médecine, consulted by the Minister of Education following the death at Boulogne in May 1848 of a perfectly healthy young man, for once followed the lead of its appointed expert, Professor Malgaigne, and subscribed to the acquittal of chloroform, only making certain precautionary rules and scheduling it as a poison (31 October 1848, 9 February 1849). In 1853, the Société de Chirurgie, called upon to take up the question on hearing a paper by Dr Vallet, of Orleans, came to the conclusion, on the advice of a report submitted by Robert, that there was no adequate justification for abandoning such an admirable discovery. In 1857, the Académie de Médecine, appealed to once more, decided that "in the present state of knowledge, apparatus might

or might not be used, and that the method of etherization could be left to the choice of the physician or surgeon."

The Lyons school, on the other hand, ranged itself firmly, with Pétrequin and Diday, on the side of ether, "a safe and harmless anaesthetic", and refused, on the pretext of eclecticism, to reconcile the two drugs.

Faced with fresh opposition on the part of the Société de Chirurgie de Paris, which had been confronted in 1859 with a paper by Dr. Hervez de Chégoin, Professor Barrier, appealing against this sentence before the Société de Médecine de Lyon, on 28 March 1859, concluded his speech with these words: "Even if ether is less prompt in its action and more disagreeable in its effects, it is infinitely less dangerous and anaesthetizes quite as well as chloroform, surgeons should therefore give their vote to ether."

In the modern development of anaesthesia—vapour narcosis (chloroform, ether, ethyl chloride), gas narcosis (nitrous oxide, cyclopropane, ethylene, acetylene), extrapulmonary narcosis (evipan), spinal and subarachnoid local and regional anaesthesia—there is a universal tendency towards the abandonment or severe restriction of chloroform, in spite of the rapidity and constancy of its action, the depth of the narcosis and the smooth return to consciousness, and towards an acknowledgment of the superiority and safety of ether, as a guarantee against the immediate primary dangers of anaesthesia (E. Forgue). This fact takes us back to the year 1847 in which etherization was adopted in France, an event of which Professors Malgaigne and Velpéau were the chief promoters.

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EARLY SURGICAL ANAESTHESIA IN SPAIN

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Ether was used as a surgical anaesthetic for the first time by Long, of Athens, Georgia, but the fact was not sufficiently widely published, and the use of ether anaesthesia can be said to have been first publicly demonstrated by W. T. G. Morton, a Boston dentist, on 16 October 1846.

In Spain the Academia de Esculapio offered among its prizes for 1847 a silver medal for the best paper on ether as an analgesic. The famous Spanish surgeon, Don Diego de Argumosa y Obregón (1792-1865) was the first in Spain to use ether as a general anaesthetic—on 14 February 1847—in an operation for the opening of an abscess of the neck, on the 16th of the same month to open an abscess of the breast, and two days later for the resection of an exostosis of the shoulder.

On 26 February, with this anaesthetic, he inserted a seton in a patient suffering from purulent ophthalmia. He reported all these uses of ether as an anaesthetic in the *Boletín de Medicina, Cirugía y Farmacia* (No. 62, 7 March 1847).

Drs Benavente, Ruiz Gimenez and Ulpiano Fernández, of the Academia Médico Matritense, as reported in vol. 2 of the *Anales de Cirugía*, inhaled ether vapour through the nose, becoming completely unconscious.

Don Ulpiano Fernández, as a result of inhaling the ether, experienced a severe coughing fit, vomiting, four or five convulsive contractions, headache and roaring in the ears, with subsequent dulling of the senses. Don Basilio San Martín explains these disturbances by the fact that Dr Fernández was a great admirer of England and the English in everything, and imitated them in the ease with which he daily drank alcoholic beverages, rum, brandy, etc. This is one of the earliest mentions of the importance of alcoholic habits in producing disturbances during general anaesthesia.

In the Madrid General Hospital, Dr Antonio Saez tried out ether as an anaesthetic (*Boletín de Medicina, Cirugía y Farmacia*, No. 63) on a woman of 50 in order to remove a scirrhus tumour of the right breast, which weighed 13½ lbs. Before using ether by inhalation, he administered it as an enema, using a drachm of ether and an ounce of distilled water, which he mixed when the enema was about to be given. This took place at 11 in the morning, after a quarter of an hour the patient felt heat in the stomach and vapours rose to the mouth. After half an hour she became stuporose. Rectal anaesthesia was also used by the great Russian surgeon, Pirogoff, in the same year, 1847.

In the Medical Faculty at Barcelona experiments were carried out on dogs, also in 1847, before ether was applied to human beings.

Dr José González Olivares, of the Santiago Medical Faculty, was one of the first in Spain to recognise the advantages of ether anaesthesia, publishing his observations in the *Boletín de Medicina, Cirugía y Farmacia* in July 1847. It was not long until the apparatus invented by Drs Argumosa and San Martín was used for this type of anaesthesia. Dr Basilio San Martín won the prize offered by the Academia de Esculapio, to which we have already referred. The paper, presented in September 1847, reported 53 personal observations, anaesthesia had been repeated several times in some patients and San Martín himself had been anaesthetized with ether 16 times. This paper was never published, remaining the property of his nephew, the well-known surgeon, Don Alejandro San Martín.

Dr González Olivares, of the Santiago Faculty of Medicine, in December 1847, operated on a carcinoma of the breast, extirpating the axillary ganglia, under chloroform anaesthesia. The operation was long and arduous. A few days later he amputated a soldier's penis, also under chloroform. Regarding chloroform anaesthesia, of which the first details had been communicated by Simpson to the Edinburgh Medical Society, González Olivares wrote: "It has not been possible to achieve with ether what has been achieved with chloroform. With the latter we have attained that which has been pursued so ardently and with such great effort" (*Boletín de Medicina, Cirugía y Farmacia*, No. 105).

These observations of González Olivares had been preceded, in the Santiago Faculty of Medicine, by experiments on dogs and rabbits. The chloroform had been prepared by Professor Casares, according to Soubeiran's method. It was later inhaled

by Professors Andrés de la Orden, González Olivares and Vicente Guarnerio

In Madrid, chloroform was prepared by the pharmacist, Don Diego Lletget. It was inhaled by Drs San Martín, Lázaro, Saralegui, Asuero, Ataide, Santero Calvo and Ulibarri. All this is recorded in the *Boletín de Medicina, Cirugía y Farmacia*, No 106, January 1848.

Don Basilio San Martín administered chloroform to a patient with anal fistula, who was operated on by Dr Bonifacio Blanco in the General Hospital. Don Basilio San Martín, referring to his own observations, says: 'Unconsciousness is reached more quickly and is of longer duration. It must be controlled with a certain amount of care. Less than the drachm recommended by Simpson should be used, even though the dose should have to be repeated. In this way choking is less and the rigidity which appears at first is rarer.'

La Verdad of 10 November 1848 publishes an article signed by Olivares in which the success of chloroform anaesthesia in two amputations carried out by Dr Francisco Martínez is reported. The chloroform had been prepared by Dr Andrés Checa.

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The use of anaesthesia in obstetrics was defended by Dr Juan Burgos Requejo at the Congress of Medical Sciences at Cádiz in August 1878.

Professor Morales Pérez, of Barcelona, used anaesthesia by hot ether from 1888 onwards, a method perfected by Dr Díaz de Llaño. By the time he came to read his communication to the XIVth International Congress at Madrid he had carried out 4,977 operations with this technique without encountering any respiratory complications.

The famous gynaecologist Fargas alternatively employed ether and chloroform in anaesthesia.

Suárez de Mendoza recommended, in 1896, what he called the 'Spanish method', which consisted in a mixture of oxygen and chloroform, the excellency of which he lauds in his booklet *La terapéutica quirúrgica a fines del siglo XIX*.

This method was continued by its author and by Dr Eulogio Cervera in the Clínica del Rosario.

It was also recommended by Professor Alejandro San Martín, with a special technique and apparatus for naso-pharyngeal insufflation of the oxygen-chloroform mixture. The chloroform never exceeded 8% of the mixture inhaled.

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ANAESTHESIA IN ARGENTINA¹

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On 18 June, 1848, John Mackenna, a native of England and surgeon to the British Hospital in Buenos Aires, announced, in the Hospital's annual report, the sensational news that 'the first operations in this city in which ether was used with success took place in our Hospital. We were thus able to confirm the surprising fact that inhalation through the mouth and nostrils of this volatile spirit produces a state of unconsciousness such that the most serious surgical operations can be carried out painlessly. Since then it has been successfully employed on several occasions, and lately a new discovery called chloroform has been used in the case of a woman whose thigh was painlessly re-fractured and reduced, with the most satisfactory results'. A few years later, Leopoldo Montes de Oca published his thesis 'Surgery in Buenos Aires during the years 1852, 1853 and 1854', part of which was devoted to anaesthesia and in particular to chloroform, a drug which, soon after its appearance, succeeded in displacing ether completely for several decades; he describes the 'rules for chloroformization' which were issued in ward 3 of the Hospital de Hombres, where his father, Juan José Montes de Oca, held the chair of clinical surgery, both had previously seen chloroform used in Río de Janeiro, where they lived in exile during the tyrannous rule of Rosas.

Until 1890 chloroform continued to be the anaesthetic of choice, and was the subject of various investigations and theses such as that of Juan Clara (1857) and Wenceslao Tello (1880) who emphasizes the advantage of administering morphine and camphor oil as coadjuvants in prolonged surgical interventions. In that year (1890), after a visit to Europe, where he confirmed its advantages, Andrés Llobet reintroduced ether in his clinic

at the Hospital Rawson, his example was followed by outstanding surgeons such as Juan B. Justo, Avelino Gutierrez, Castano y Revilla of the Hospital San Roque, and Palma of Professor Gandolfo's unit in the Hospital de Clínicas, but in a short time, possibly because of difficulty in obtaining ether, they reverted once more to chloroform. In 1895, Julio Paz, of the Hospital de Clínicas, used ethyl bromide for the first time in operations of short duration.

The earliest papers on spinal anaesthesia appeared at the beginning of the present century and Bartolomé Podestá, with his thesis of 1901, was the first to publish a large number of cases: the method quickly became popular, and was practised by other surgeons of note, among them Gutierrez, Decoud, Finochietto, Arce and Repetto.

In 1904, Robert Halahan, surgeon to the British Hospital, introduced the first apparatus for the administration of nitrous oxide and oxygen, but, owing to difficulty in obtaining the gas, it was several years before its use became widespread. Artemio Zeno de Rosario employing it in 1916 and Rodolfo Pasman a little later. About 1911, and throughout the European war, the efforts of Pedro Chutro resulted in ether's once more taking pride of place among anaesthetics, especially after the introduction of Ombredanne's apparatus, but later, owing to the scarcity of experienced anaesthetists, narcosis was replaced in many hospital clinics by other methods more easily controlled by the surgeon himself, such as spinal, local, regional and epidural anaesthesia: the last of which was particularly recommended by Professor Alberto Gutierrez.

In 1934, Doctor Teófilo Meana de Casilda sent his assistant Robert O. Elder, to study the methods of anaesthesia used in the United States and on his return they began, to a great extent, to use nitrous oxide, ethylene and later cyclopropane. The beginning of the era of specialization in the subject was marked, in particular, by the introduction in 1936, of a course for post-graduates directed by the Mexican professor, Federico Volbrecht-Hausen, in the Hospital de Clínicas, and by the initiative of Doctor Jose Arce, director of the Instituto de Cirugía Clínica, where the first hospital department of anaesthesia was established: the forerunner of many others now functioning in different hospitals.

¹ Translated from the Spanish by M B W.]

THE ETHER DISCOVERY IN AUSTRIA AND GERMANY

In 1926 Dr I Fischer, who died in England in 1943, published in the *Wiener klinische Wochenschrift* (39, 52-54) an account of the reception of the ether discovery in Germany and Austria. According to Fischer, the first news in Germany of the discovery was published, not in a medical periodical, but in the old-established *Augsburger allgemeine Zeitung* (10 January 1847). This journal based its information on reports published in "Mehrere Londoner Blätter, namentlich auch die Medical Review". Fischer says that this notice was undoubtedly the source from which the Viennese professor of surgery, Franz Schuh, obtained his first information of ether narcosis, which led him to become the first German-speaking surgeon to employ the new procedure. However, the fact that his information was from a newspaper, and not from a medical periodical, was sufficient to make Schuh proceed with considerable caution, and he carried out preliminary experiments on dogs, not only with a view to testing the narcotic action of ether, but also in order to convince himself of the harmlessness of the procedure. Shortly afterwards, Schuh reported on the results obtained in 21 surgical operations, and he was able to say that individual susceptibility to ether varied, drinkers and those under the influence of great apprehension being the most difficult to narcotize. As a result of Schuh's publications, a number of other Austrian surgeons adopted ether anaesthesia.

Apart from the interest in medical circles, there was also a considerable popular interest in the discovery as exemplified by reports in the general press. In an article on 2 February 1847, the Vienna correspondent of the *Augsburger allgemeine Zeitung* closes, unidiomatically and rather inappropriately, with the words "forever Jackson" rather inappropriately, with the Opposition to ether soon became manifest in certain quarters, and on 24 March 1847 there appeared an anonymous communication uttering a warning against the indiscriminate use of ether for surgical operations. On 15 May, the Viennese professor of chemistry, A. M. Pleischl, spoke of the numerous dangers implicit in ether narcosis, and postulated harmful effects on the brain, spine and nerves of the fat-solvent property of ether. He also maintained that the blood must be adversely affected by the power of ether to coagulate albumin, and from the "moral" point of view he characterized the new procedure as "unworthy". Even Schuh, originally an enthusiast, later warned against the too-frequent use of ether narcosis, which he himself employed with diminishing frequency.

A few months later Simpson's introduction of chloroform narcosis caused a similar outbreak of professional and public interest in the new anaesthetic agent.

N H J

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INTRAVENOUS INJECTION AND ANAESTHESIA

Harvey's elucidation of the circulatory process provided a study of absorbing interest, and during the second half of the seventeenth century many experiments arising from it were made. During the late sixteen-fifties "the learned and ingenious Dr Christopher Wren did propose in the University of Oxford to that noble benefactor to experimental philosophy, Mr Robert Boyle, Dr Wilkins and other deserving persons, that he thought he could easily contrive a way to convey any liquid thing immediately into the mass of blood, videlicet by making ligatures on the veins, and then opening them on the side of the ligature towards the heart, and by putting into them slender syringes or quills, fastened to bladders (in the manner of clyster-pipes) containing the matter to be injected, performing that operation upon pretty big and lean dogs, that the vessels might be large enough and easily accessible".

Mention occurs in volume 1 of the *Philosophical Transactions* (1665, p 128) of experiments in which Boyle injected opium and crocus metallorum (impure oxysulphide of antimony) into the hind legs of dogs, "whereof the success was, that the opium, being soon circulated into the brain, did within a short time stupify though not kill the dog, but a large dose of the crocus metallorum made another dog vomit up life and all".

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In 1665 J S Elsholtz published in Berlin his *Clysmatica nova, oder neue Clystier-Kunst, wie eine Arznei durch eröffnete Ader bey zu bringen, dass sie ihre Wirkung eben also verrichte, als wan sie durch den Mund genommen worden wäre*. Clinical injections of laxatives and other medicaments done by Fabricius and others in Danzig were reported in the *Philosophical Transactions* during 1667 and 1668.

The method was referred to in 1833 by François Magendie in his *Precis élémentaire de physiologie* (2, 432 et seq.). He recounted a recent experiment in which an American named Hales had made himself very ill by injecting castor-oil into his veins. Magendie commented, "the injection of medicaments into the veins may be regarded to-day as the only effective resource in some extreme cases where the ordinary aids of medicine are insufficient".

In 1842, four years before the general adoption of surgical anaesthesia, R M Glover reported in the *Edinburgh Medical and Surgical Journal* some experiments in which he had injected chloroform and bromoform into the veins of animals. He noticed, among other things, that some of the animals became stupefied. But when, in 1847, P J M Flourens injected ether into the arteries of dogs, he found that although the animals became "drunk," anaesthesia was not produced. Two years later (1849) Thomas Nunneley, of Leeds, injected sulphuric and acetic ether and chloroform intravenously into dogs. He found that "the symptoms preceding death, and the appearance presented afterwards, do not differ materially from those caused by inhalation".

In 1874 Ore, of Bordeaux—having made preparatory tests on dogs during 1872-73—first produced surgical anaesthesia in man by intravenous injection. He used about 10 g of chloral hydrate in 30 g of water. The success of Ore's early cases, e.g. the removal of a finger-nail and the excision of a diseased testicle, led others to try his method, but fatalities occurred and by 1877 intravenous anaesthesia had been discredited.

It was not revived in clinical practice until 1909, when Ludwig Burkhardt, of Würzburg, successfully used a saline solution containing 5% ether. Kummell, in Germany, Honan and Hassler, in America, and Felix Rood, in England, also adopted this use of ether.

By 1912 the intravenous route for general anaesthesia was well established and a variety of anaesthetic agents gradually came into use—among them were hedonal (introduced by Fedoroff in 1911), paraldehyde (Noel & Souttar, 1912), certain barbiturates (the first was somnifene, used by Bardet in 1923), and alcohol (Marin, 1929).

B M Duncum

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RECTAL ANAESTHESIA

The sedative enema is very old. Referring to the virtues of garden poppies, John Gerard, in *The Herbal* (London, 1633) wrote "The leaves, knops and seeds stamped with vinegar, woman's milke and saffron and put in the fundament as a cluster causeth sleepe", and writing of *Hyoscyamus niger* "To wash the feet in the decoction of henbane causeth sleepe or given in a cluster it doth the same".

During the first few months of 1847, at the time of the general adoption of sulphuric ether as an inhalation anaesthetic, J G Vicente y Hedo, and Marc-Dupuy (apparently at the suggestion of the Parisian surgeon P J Roux) tried the effects of liquid ether introduced into the rectum of animals. Marc-Dupuy, who mixed water with the ether, found that in dogs the injection produced rapid and satisfactory anaesthesia with only slight inflammation of the rectal mucous membrane. He concluded that etherization might more safely be carried out by way of the rectum than by inhalation.

While these experiments were in progress Nikolai Ivanovich Pirogoff, professor of surgery at St Petersburg, reported to the Académie des Sciences in Paris his very successful clinical use of ether vapour insufflated into the rectum. His apparatus consisted of a container for 1½ to 2 ounces [45-60 ml] of liquid

ether (surrounded by a warm water jacket), joined to a rubber catheter through which the vapour entered the rectum. The rectum itself was simply washed out as a preliminary to insufflation.

After ether had been superseded by the more easily manageable anaesthetic chloroform, in November, 1847, rectal anaesthesia was neglected until about 1882, when it was revived by the surgeon, Oscar Wanscher, of Copenhagen. His method was essentially the same as that devised by Pirogoff, but to avoid the danger of the ether vapour condensing *en route* between the warmed vaporizing bottle and the rectal cannula, he warmed the connecting tube also. A paper on rectal etherization, read by Wanscher at the International Congress of Medicine, held in Copenhagen in 1884, attracted some attention, particularly as ether was not in general use in continental Europe at that time (in fact, Lyons, during the nineteenth century, was almost the only European surgical centre where ether had remained the anaesthetic of choice).

Earlier in the same year (1884) a fellow-citizen of Wanscher's, Axel Yverson, when visiting Lyons, had asked the surgeon, D. Mollière, whether he administered ether by the rectal or the respiratory route. The question prompted Mollière to try rectal etherization, and the news of his success with it reaching America during the late spring of 1884, it was also enthusiastically tried there by W. T. Bull, Weir, and others.

In England, the specialist anaesthetist, D. W. Buxton, adopted rectal etherization about 1890 using it especially in operations involving the head and neck because of the unobstructed operating field which it allowed the surgeon. Buxton's apparatus included a glass globe in the tubing behind the rectal cannula, to intercept liquid ether.

During the first decade of the present century various improvements continued to be made in America in the technique of rectal anaesthesia, the most important work being done by J. H. Cunningham in Boston and by Sutton in Kansas City. It was this work which, so J. T. Gwathmey stated, prepared the way for his introduction in 1913 of oil-ether colonic absorption anaesthesia.

B. M. Duncum

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SURGICAL ANAESTHESIA THROUGH MESMERISM

About the middle of the seventeenth century, the Jesuit Athanasius Kircher of Fulda described an experiment in which a hen was persuaded to lie motionless on a pavement by working upon her imagination. First her feet were bound and she was allowed to struggle until she became convinced that escape was impossible, and lay still. A straight chalk line was then drawn away from her eye along the pavement and when her feet were untied, still believing herself a captive, she did not move.

In his *Magnes sive de arte magnetica* (Rome, 1654) Kircher devoted a section to the curative powers of magnetic substances, and it was while studying magnetism, rather more than a century later that Franz Anton Mesmer concluded that the human hand could exercise such powers, and evolved his cult of animal magnetism—afterwards called mesmerism.

Mesmer's bizarre seances, held in Paris during the late seventeenth seventies, brought him into disrepute, and after the French Revolution he himself vanished from the public eye. Nevertheless mesmerism continued intermittently to exert its curious attraction for the credulous layman and to interest a certain number of medical men.

In 1829 the French surgeon, Cloquet, removed a cancerous breast from a Madame Plantin, the lady's physician having induced in her a state of 'sommnambulism' in which she was able to converse with Cloquet during the operation, yet felt no pain and afterwards remembered nothing of what had taken place.

In October 1842 a well-authenticated case was reported from Nottinghamshire, in which a barrister named Topham induced a mesmeric sleep in a man whose leg was then amputated at the thigh. Topham described how the surgeon 'after one earnest look at the man, slowly plunged his knife into the thigh, directly to the bone' and then made a clean incision round the bone to the opposite point, on the inside of the thigh. The stillness at this moment was something awful the calm

respiration of the sleeping man alone was heard. Soon after the second incision, a moaning was heard from the patient, which continued at intervals until the conclusion. It gave me the idea of a troubled dream, for his sleep continued as profound as ever." Questioned on his awakening, the patient said, 'I never knew anything more, and never felt any pain at all, I once felt as if I heard a kind of crunching.' This, Topham thought, was probably the sawing of his thigh-bone.

During the late eighteen thirties John Elliotson, professor of the practice of medicine in the University of London, had become interested in mesmerism, accepting some of the occult as well as the rational beliefs connected with it. This brought upon him the disapproval of his colleagues, and in 1838 he was compelled to resign his professorship. In 1843 Elliotson published a record of *Numerous cases of surgical operations without pain in the mesmeric state*, and in 1846 he founded a Mesmeric Infirmary in Bedford Square, London.

Elliotson's work aroused the interest of James Esdaile, of the Hooghly Hospital, Calcutta, and in 1845 he mesmerized and operated painlessly on two occasions on a Hindu convict. Nine other painless operations were witnessed by a special committee appointed by the Deputy Governor of Bengal, and as a result Esdaile gained Government support for his activities. In all he recorded 261 painless operations the death rate being about 5.5%.

Despite the unquestionable integrity of exponents such as Esdaile mesmerism was violently attacked, particularly by medical men. A reasoned defence of the "ordinary manifestations—especially the cataleptic state in which patients were insensitive to surgical pain—was published by John Forbes in 1845. At the same time he condemned belief in the extraordinary phenomena such as clairvoyance.

In December, 1846 the *London Medical Gazette*, a bitter critic of the mesmerists, announced the news of Morton's use of ether anaesthesia under the heading, "Animal Magnetism Superseded—Discovery of a New Hypnotic." Although mesmerism was indeed superseded, rare cases of its use to produce surgical anaesthesia continued to be reported during the remainder of the nineteenth century.

The most important name connected with mesmerism is that of the physician, James Braid, who approached the subject in 1841 in a spirit of scepticism. He soon became convinced that a state of abnormal sleep could be self-induced by gazing fixedly at some bright object ('I generally use my lancet case,' Braid stated) held about 8 to 15 inches [20-38 cm.] from the eyes and a little above eye level. This method he called *neuro-hypnotism*, and used it to get patients into a suggestible state for the treatment of physical and mental ailments, e.g. constipation and melancholia. On one or two occasions he extracted teeth from hypnotized patients.

Braid's method of hypnosis was introduced into French medical practice by Azam and Broca in 1859. Its application in the treatment of nervous disorders was intensively studied by Charcot in Paris and by Liebeault and Bernheim at Nancy.

From these beginnings psychotherapy evolved.

B. M. Duncum

845

THE HISTORY OF SURGICAL ANAESTHESIA

Under the above title, Schuman's of New York has published a history of anaesthesia by Major Thomas E. Keys. This work has developed from a chronological table illustrating the history of anaesthesia which was published in 1942 in Lundy's *Clinical anaesthesia*. The author also used the material on which the chronology was based for a series of five papers on 'The development of anaesthesia,' published in *Anesthesiology* during the years 1941-1943. Later a selection of important references arranged by subject was published in two instalments in *Current Researches in Anaesthesia and Analgesia*. Finally and at the suggestion of Professor Chauncey D. Leake, the author revised his material for publication as a book.

The repeated opportunities of revision and re-assessment of material and the fact that Major Keys has been reference librarian to the Mayo Clinic assistant to the Librarian of the

Army Medical Library at Washington, and officer in charge of the Cleveland branch of the Army Medical Library, would amply justify the expectation that this should be a book which would be proof against the most pedantic and ungenerous criticisms, but this expectation is not entirely fulfilled.

It can be said at once that by all ordinary standards this is a very good short history, and that by any standards it is an unusually attractive book. The publishers have contributed greatly to its attractiveness by the attention that they have given to typography and production. There are 42 illustrations, including one of Paul Bert's extraordinary travelling anaesthesia-chamber (facing p 75). The overall length of the book is xxx + 191 pages, but of these no more than 92 are occupied by Major Keys' history. The remainder of the volume is devoted to a preface, an introductory essay by Professor Chauncey D Leake, a chronology (24 pages), a list of references by subject (24 pages) and another by authors (20 pages), a chapter by Dr N A Gillespie on the future of anaesthesia, and an appendix by Professor J F Fulton on the Morton and Warren tracts on ether (Letheon).

The book is dedicated to Dr J S Lundy, who is described as "warrior against pain". To the reader who is accustomed to a more impersonal style of historical writing, the romantic exuberance betrayed in the terms of this dedication and in other parts of the book is likely to be irritating. Much as we may esteem Professor Leake's reputation as a pharmacologist and medical historian, not all of us will wish to be involved in the intimacies implied by the use of the familiar names of his colleagues—as, for example (p xxx), "Art Guedel", "Norm David", "Nil Phatak", and "Joe Swim". Nor does the "royal gastronomic welcome of the anaesthetists of San Francisco" (p xxix) seem to have much relevance to the history of anaesthesia. Although custom and prejudice enter largely into our attitude about these things, there is rather more in it than that. We feel that there is a certain lack of self-criticism involved, and this causes some lack of confidence in the rest of the matter. This lack of confidence is intensified when we find (p xxi) "Dr J M MacIntosh" where "Dr R R Macintosh" is obviously intended. Further, although the author says (p xi) that he has seen as his responsibility "the correcting of many of the errors that have crept into the history of anaesthesia", and affects the rather pretentious word "historiography" in connection with his own work, he has not avoided the perpetuation of errors by failure to consult original sources. It is twice stated (pp 38 and 106), for example, that Alexander Wood, of Edinburgh, first injected morphine subcutaneously in 1843, whereas a closer study of the literature would have revealed that this is an incorrect date which had its origin in a misprint in one of Wood's own papers. The correct date is 1836. Similarly, it is incorrect to say (p 38) that Lafargue in 1836 "injected morphine paste subcutaneously" by means of a "needle trocar". Lafargue used at this time a vaccination-lancet, the extremity of which was smeared with morphine paste. Again, the claims of Taylor and Washington to priority of subcutaneous injection are given without mentioning the fact that they were made retrospectively, some years after Wood's publication. From Major Keys' version of this story, one would assume that Wood had merely developed a method which had been originated by Taylor and Washington. Pravaz, as usual, is erroneously credited (p 107) with the "invention of the hypodermic syringe" in 1853. However, on the main subject of surgical anaesthesia, the author has, judging from his list of references, placed more reliance on first-hand sources. "Won't my readers please advise me of [important omissions] and of other ways to improve this book?" pleads Major Keys in his preface. Although we have been unable to resist this plea, we do not regard some minor defects as fundamentally affecting the value and interest of this book.

N H J

FOLKLORE OF ANAESTHESIA

Ancient anodynes primitive anaesthesia and allied conditions,
by E S Ellis
The subject of this book is one of exceptional interest. In

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ancient writings there are a number of allusions, some of them very familiar, to what would appear to be attempts at the production of a state equivalent to surgical anaesthesia. There are also travellers' tales of the use of stupeficients to dull the pain of cutting-operations of various kinds. It has been said, for example, that chewed coca leaves were used by Peruvian Indians as a local anaesthetic.

Unfortunately there are difficulties in the way of attributing much significance to the allusions by ancient writers. In the first place, it has often been impossible to identify with certainty the plant or substance used, and in the second place the agent, when identifiable, often possesses no known narcotic or local anaesthetic properties. Light might be thrown upon this difficult question by detailed studies of a few selected allusions in the literature, and by field investigations among primitive peoples. But a mere multiplication of inherently unsatisfactory evidence can throw no light upon the problem. It is this approach that Dr Ellis has adopted. Although he has gone to considerable pains to locate and collate references to possible examples of primitive anaesthesia, the result is that he leaves the problem almost where he found it.

The book is not an easy one to read because it lacks plan or continuity. It gives the impression that a great part of it consists of random notes assembled together in an order which has been determined by accident or caprice. The book is divided into chapters on anaesthesia by physical means, psychological anaesthesia, inhalation, anaesthesia by known drugs, by unnamed and various drugs, local anaesthesia, anaesthesia in different countries, and modern anaesthesia. It is typical of the lack of system of the book that Henry Hill Hickman's experiments on inhalation anaesthesia are included in the chapter on "Anaesthesia by physical means", instead of in that on "Modern anaesthesia"—or even in the chapter entitled "Inhalation".

The literary style is strange, and there are some passages which resemble remarkably the unconsciously-funny answer of a schoolboy to a question in an examination paper. Thus, we are told (p 18) that

"The Yogis of India practise a philosophy which they call Yoga, it consists largely of breathing exercises and the whole system is called Pranayama."

Again (p 68)

"Certain magical properties were also attached to mandragora and at the trial of Joan of Arc in 1431 she was accused of carrying a mandrake in her bosom which she denied. King Solomon and Alexander the Great are reputed to have derived help from the same source."

And (p 88)

"Rosita Forbes says that the Sitt, meaning a woman who makes her living by castration, in Harar, Abyssinia, used to use an anaesthetic made from an infusion of poppies and Kat."

There is also a capriciousness in the forms of proper names, as in Carden (p 23), Cardanus (p 38) and Cardan (p 40). Examples such as these, and particularly the disregard of punctuation, make us wonder whether the proof-reader may have been engaged in some attempt at primitive anaesthesia.

The oft-repeated fallacy of "the invention of the hypodermic syringe" by Pravaz appears on p 45. Pravaz never in his life gave a hypodermic injection, although he experimented on animals with a form of intravascular sclerosing therapy.

Some of the author's assertions are pharmacologically very questionable—for example, that belladonna "depresses the sensitivity of practically all nerves". However, the most extraordinary example of the author's uncritical attitude is the statement (p 84) that a remedy for whooping-cough which is "sound in theory and practice" is "to cut up some garlic very small and place it in the patients' socks". The author adds "As he walks about, the garlic will work into his skin and very often be highly beneficial to a spasmodic cough. One of the leading drug houses has, or had till a short time ago, a mixture containing garlic which would sometimes cure a cough when nothing else would."

Uncritical enthusiasm is displayed by the inclusion of highly irrelevant observations, which appear to be regarded as contributory evidence. For example, in discussing whether urine might have any narcotic or inebriant properties, the author includes (p 96) the following observation

"Bourke describes a kind of orgy of urine drinking among the Zuñi Indians and it is difficult to see why the guests should

have assisted at it if they did not get some sort of 'kick' out of it somewhere."

Stated in more formal terms, the author's argument is (i) Nobody would drink urine for any reason but that it was inebrant, (ii) the Zulu Indians drank urine, therefore (iii) urine is an inebrant.

In the same section, the following entirely inconsequential and inconclusive anecdote is given (p. 97)

"Mr Hampton, a well known pharmacist in Gloucester, tells me that a man of considerable education and social position told him that he was in the habit of drinking his own urine, unfortunately it was so long ago that Mr Hampton does not remember his reason for so doing."

As a further example of the sort of "evidence" by which contentions are supported, the author refers to an inscription in an Aesculapian temple recording a surgical operation. He comments

"though no drug is mentioned, this is where it is difficult to see how a drug could possibly have been omitted."

FILMS

This article is the second in a series by medical men or biologists who have had practical experience in the production of films of medical interest. Dr Organe has been largely responsible for the success of a series of medical educational films which is generally regarded as establishing a precedent. For the first time, a series of films comprehensively covering a branch of clinical medicine has been made by the close co-operation of a professional film-unit and a hospital department. The films were produced by Imperial Chemical Industries Ltd in collaboration with the department of anaesthesia of the Westminster Hospital, London.

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THE MEDICAL DIRECTION OF A SERIES OF FILMS ON ANAESTHESIA

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It can rarely have fallen to the lot of a teacher to be afforded the opportunity of making a series of films covering many aspects of his subject. Expense alone is prohibitive to the private individual who is not also an expert cinematographer and technician. Such an offer is apt to be accepted by the uninitiated with a light-hearted enthusiasm. The light heart soon grows heavy with the dawning realization of the immense amount of work involved, the enthusiasm or, more accurately, the sense of the importance of the task in hand endured, in this case, the two years or so taken for its completion.

Scope of Films in teaching Anaesthesia

The art or, as it may become, the science of anaesthetics is not a subject that lends itself easily to presentation in the lecture theatre. It should, ideally, be taught by practice under supervision. Unfortunately, suitable material is limited, the ground which should be covered is extensive and the behaviour of patients under anaesthesia is unpre-

On p. 108 the statement is made that Peruvian Indians "fill a wound with powdered cocoa [sic] leaves, which contain some 9 per cent of cocaine."

It is difficult to believe that the yield of cocaine from powdered coca leaves would be anywhere near as high as 9%, or that the use of such a high concentration of cocaine on an open wound could be attended by any but the most disastrous consequences. Presumably the figure given is a misprint.

The author appears to subscribe to the view that the application of belladonna to the unbroken skin relieves pain. The continued use of belladonna plasters implies that he is not alone in this absurd and unwarrantable belief.

Apart from the criticisms made above, the book contains some interesting material which is evidently the fruit of extensive reading and enquiry. It can, however, hardly be said to justify the publisher's claim on the dust-wrapper that it is "a valuable work of reference for all who are interested in the anthropological and social aspects of medical history." (For price and other details see *BMB* 859)

N H J

dictable. Many important points are unavoidably missed as it is not possible to organize a series of graded demonstrations as can be done, say, in the physiological laboratory. Further, it is always difficult to compromise between the interests of the patient, who should always have the best available treatment, and those of the student. Under the guidance of his teacher, he may never meet with serious difficulty and he will, therefore, be quite unfitted to deal with a grave emergency when, after qualification, he meets one for the first time. Yet, theoretical instruction must precede practical experience if he is to gain the greatest benefit in the short time allotted to the subject.

Here seemed to be an opportunity at once to relieve the tedium of the lecture and to demonstrate those hair-raising difficulties which mean life or death to the patient but which the experienced anaesthetist can take in his stride.

The Film Unit

We were fortunate, and also limited, in having assigned to us a professional documentary film unit. To appreciate our fortune one need only compare this series of films with any yet made by amateurs as regards quality of photography, of cutting and of assembly. To explain the limitations I must describe the organization of the unit assigned to each film. In charge is a director—and assistant—who is responsible for the script, for the supervision of the photography, the cutting, the final assembly of the film and of the spoken commentary. There is also the camera-man—sometimes two of them, each with an assistant. The 35 mm cameras are cumbersome and must be supported on a tripod, so, also, are the three or four lamps.

The presence of this small army, unaccustomed at first to the refinements of operating theatre technique, and of their impedimenta, place a strain on the less camera-minded surgeons. Added to this is the not unnatural but quite unreasonable—and not always silent—resentment of some of the nursing staff at such frivolous innovations.

Planning the Series

We started with a programme of eight subjects. Two of these propagated by binary fission (there is, apparently, a limit to the tolerance of a student audience at any one session) and one was added. An expected total of two hours' running time expanded to about five hours, and much of importance was yet left unsaid.

**FIG 1 ENDOTRACHEAL ANAESTHESIA
PERORAL INTUBATION**



Print from the film on *Endotracheal anaesthesia* (for review, see BMB 851) The anaesthetist is passing the endotracheal catheter by visual control with a laryngoscope

**FIG 2 ENDOTRACHEAL ANAESTHESIA
NASAL INTUBATION**



Print from a sequence in animated diagram The success of this procedure depends mainly on the correct position of the head. The course of the air-passage from nostril to glottis is curved. When a tube which has a similar curve is passed through the nose it tends to follow this curve and enter the trachea

At an early stage came the realization that, as these films were to go to many countries and to be used by many teachers, one's own opinions, however much one felt them to be in advance of the times, must be replaced by views acceptable, on the whole, to the majority though in their entirety not even to oneself. It was also realized that, as no two experts hold identical views, the chief responsibility for each film must rest on one individual.

The first stage in production was the draft of a lecture designed with a view to illustration by appropriate action. From this material the director prepared a draft shooting-script from which again, after discussion and emendation, emerged

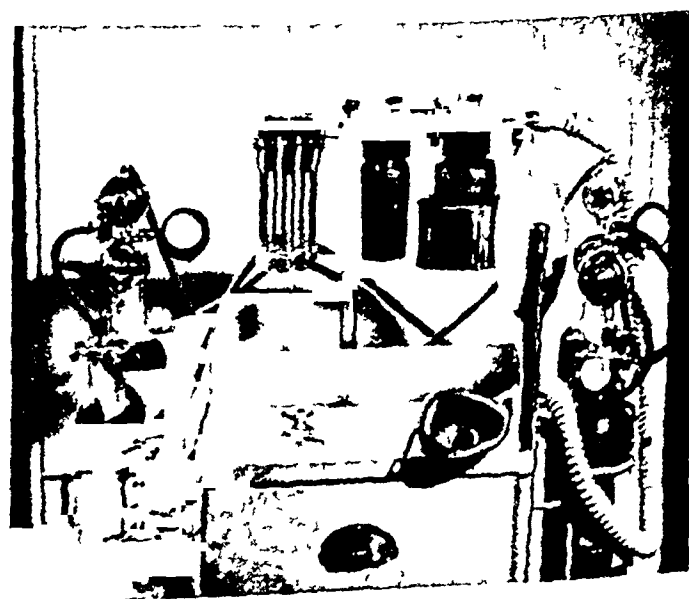
the final shooting-script. This last was modified from time to time as fortune presented the opportunity to shoot some scene which was too good to omit but which had not been included in the original version, or as it was found impossible to present some feature in the form that had been planned.

Production Problems

Unless one has a very clear idea of what stages of any particular procedure are to be photographed, at what range and from what angles, one is likely to find that some essential points have been missed and that a whole sequence, often representing many hours' work, has to be repeated. Here it is that close liaison between expert and director is essential for the work to be planned in detail. Even so, it is only after each has acquired some experience that it becomes possible to judge how much can be done within the limits imposed, in this case, by the patience of the surgeon and by consideration for the well-being of the patient. It has been suggested that medical films would be better directed by a doctor, I do not feel that, unless he is himself an expert in the particular subject, he would be better able than an intelligent layman to interpret the ideas of the author. The necessity for working to a script applies equally to the amateur cinephotographer. Obviously, when recording, say, successive stages of a plastic operation in an individual patient, there can be no going back to fill in gaps.

It is advisable for the rough prints of the day's shooting to be seen by the medical expert as well as by the director. Of a number of alternative shots, one may be better from the teacher's point of view, or a shot that is technically excellent may not show sufficiently clearly the point to be illustrated and may even be misleading. For example, one shot illustrating the withdrawal of local anaesthetic solution from a rubber-capped bottle into a syringe gave the impression

**FIG 3 NITROUS-OXIDE, OXYGEN, ETHER
ANAESTHESIA THE APPARATUS**



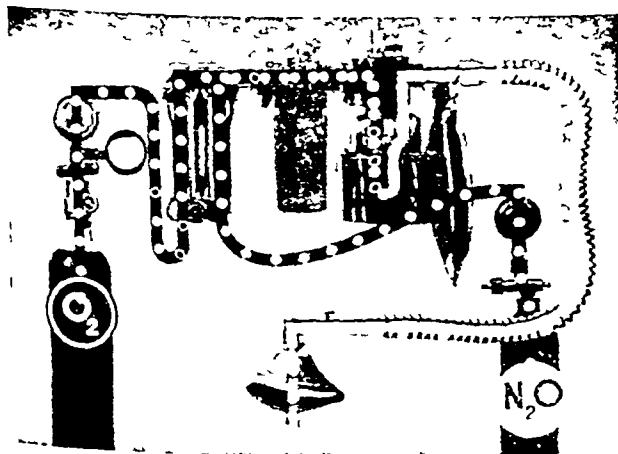
Print showing typical apparatus designed to deliver a continuous flow of nitrous oxide and oxygen, to which ether can be added as required. (From the film *Nitrous oxide, oxygen and ether anaesthesia* required. For review, see BMB 850)

that the operator's sterile gloved hands had touched the top of the bottle. This sequence had then to be repeated from another angle which would avoid this impression. Sometimes these faults of presentation will escape those who are too intimately concerned. As a corrective, all these films were shown in a rough state to students, both undergraduate and postgraduate, and most of them to teachers. In spite of these precautions some errors have remained. When the final version has been prepared, with commentary added, further amendment is almost impossible.

The production of the average documentary film seems to be a relatively leisurely affair with ample time available for setting up of lights, focusing and loading of cameras and so on—and ample time is needed! The lamps and cameras must be readjusted and the last refocused for each individual shot. The readjustment may take ten minutes or more for an exposure of a few seconds. Where a surgical operation is in progress, the patient's interests set a limit to this, and we were fortunate that much of our work was done with a cameraman whose rapid guesswork produced results that were often brilliant and always adequate. On one occasion a more orthodox cameraman was hurried because the surgeon was impatient of the delays, with the result that the whole of the afternoon's shooting was out of focus! Where shots were needed, from different angles, of relatively transient happenings, we found it necessary to have more than one camera, each poised at a selected vantage-point. The less important matching-shots, where the operation did not come into the picture, were filmed, as far as possible, on conscious subjects. In other cases volunteers were used. Some members of the film unit were anaesthetized many times and came up smiling—after a suitable period for recovery!

The ordinary black-and-white film was used and it is surprising how much can be conveyed, in this medium, of a subject that seems to call for reproduction in colour.

FIG 4 NITROUS-OXIDE, OXYGEN, ETHER ANAESTHESIA THE APPARATUS



Print from a sequence in animated diagram. The white dots represent the flow of nitrous oxide and the white rings represent the flow of oxygen from the cylinders to the flowmeters.

FIG 5 MODEL OF "HEAVY" SPINAL ANAESTHESIA



Print from the film *Spinal anaesthesia* (for review see BMB 7747). A simple model for demonstrating the uses of hyperbaric (heavy) and hypobaric (light) solutions. This demonstration portrays the distribution of 'heavy' nupercaine (0.5% with 6% glucose) in the subarachnoid space.

FIG 6 LOW SPINAL ANAESTHESIA



For low spinal anaesthesia 0.5 cm³ of heavy nupercaine is injected between the third and fourth lumbar vertebrae giving an area of anaesthesia 2.6 inches (about 5-15 cm) around the anus. For anaesthesia including the first lumbar nerve 1 cm³ is used with a little barbotage.

Apart from difficulties of supply at the time Kodachrome¹ is not available in larger size than 16 mm and Technicolor requires an enormous camera, very accurate focusing and exposure, and a vast battery of lights that would strain the tolerance of the most good-natured surgeon. For technical reasons, 35 mm film was used although many of the shots

¹ [The British Council decided some time ago to pursue the production of a film on plastic surgery. As an experiment this film made by a small film unit has been shot entirely in Kodachrome (16 mm).—Ed.]

copies were to be printed on 16 mm. For amateurs the 16 mm film is more satisfactory and has the advantage that the necessary apparatus is both less expensive and more easily handled. A 16 mm camera can, if necessary, be held by the operator, though better results will be obtained if it is mounted on a tripod.

Animated diagrams were used freely. There is much that can be conveyed in no other way, but this is a method that is beyond the scope of most amateurs. It is technically difficult and excessively time-consuming—one film waited over eight months for the completion of the animation. It is difficult for the unimaginative author to explain his ideas, many delays were caused by this lack of rapport and by the clash between the artistic sense of the animator and the purely utilitarian outlook of the medical expert, who looks, chiefly, for something approaching anatomical representation.

The Recorded Commentary

Last of all comes the recorded commentary—a much more satisfactory medium of exposition than the printed sub-title. The draft is prepared by the director from the shooting script, shredded and re woven by the medical expert, and re-edited by the director to fit the timing of the appropriate sequences. It was disconcerting to find it an axiom of the documentary-film world that no subject may be expounded

that is not at the same time illustrated on the screen. One had hoped to be able to amplify the lecture and to soften some of the more dogmatic statements—to have illustrated all the alternative views would have made the films interminably long. It was, however, occasionally found possible to interpolate a few words of explanation against a background of comparatively unimportant action.

Many potential difficulties were avoided by the fortunate accident that my own voice was found to be suitable for reproduction. Where a commentary is highly technical it is better spoken by someone familiar with the jargon. It reduces the tendency to misplaced emphasis and to the speaking, as it were, in inverted commas, of a phrase or term that is unfamiliar to the commentator though it may be elementary to his audience. There is no great skill required when, as here, the commentary is recorded without the film. A "fluff" can be covered by repetition, after a pause of two or three seconds, and the best version is selected in the cutting room. I would advise the commentator to simplify his script as far as he can. The elegant phrase may prove an insuperable tongue-twister in front of the microphone.

This account of some of our difficulties may help others to avoid them, but the amateur must expect many disappointments and much wasted time and material in his early attempts at film production.

[Overseas medical teachers and medical societies who wish to borrow or purchase prints of the films indexed or reviewed here should apply to the nearest British Council representative (see page four of cover) or direct to the Editor, quoting the numbers used below, e.g. Film 848. Inclusion of a film in this section does not imply that a print will be available for loan or purchase. In some cases it will be, and in others it will not.]

THE I C I ANAESTHESIA SERIES

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No. 4 THE CARBON DIOXIDE ABSORPTION TECHNIQUE

For review see BMB 728/1

No. 6 & 7. INTRAVENOUS ANAESTHESIA (Parts I & 2)

For review see BMB 774/6

No. 8 SPINAL ANAESTHESIA

For review see BMB 774/7

No. 9 RESPIRATORY AND CARDIAC ARREST

For review see BMB 728/2

★

848 No. 1: Signs and Stages of Anaesthesia

made by Realist Film Unit, 1945, owned by I C I, 16 mm sound, 850 ft (260 m), 35 mm sound, 2130 ft (640 m), black and white; 24 minutes

In this film the signs of anaesthesia are illustrated both by the demonstration of actual anaesthetized patients and by means of an ingenious animated diagram. The student is introduced to the various stages of anaesthesia and is shown the signs by which they may be recognized. Particular stress is laid on the value of the observation of the breathing as a guide to the depth of anaesthesia. The subject is presented clearly and with imagination, but the film is a little too long and contains rather too much diagram work.

A F-C

849 No. 2: Open Drop Ether

made by Realist Film Unit, 1944, owned by I C I, 16 mm sound, 1110 ft (330 m), 35 mm sound, 2780 ft (830 m), black and white, 31 minutes

This film is a careful demonstration of the technique of induction and maintenance of anaesthesia by the open drop method. The essential apparatus required and its manipulation are first shown and then the accessory apparatus. Emphasis is laid on the value of premedication, reassurance of the patient, and the necessity for reference to the patient's records and clinical notes before starting induction. The technique of induction is then shown with great care, and the appearance and recognition of the four stages of anaesthesia are demonstrated in detail. The film ends with a note of caution, describing how to avoid struggling in the second stage and how to deal with this should it occur. This is probably the best film in the whole series, and certainly the most useful to the majority of practitioners who are called on only in an emergency to give an anaesthetic.

B S

850 No. 3: Nitrous Oxide, Oxygen and Ether Anaesthesia (Continuous Flow)

made by Realist Film Unit, 1944, owned by I C I, 16 mm sound, 960 ft (290 m), 35 mm sound, 2410 ft (720 m), black and white, 27 minutes

A diagram of the apparatus shows its constituent parts, the gas-flow circuit, and method of charging with ether-vapour. Next, the real equipment is shown, and the routine, which must be adopted each day before it is used, of testing every component. The patient is brought in, and after the anaesthetist has reassured her, verified her clinical condition and her charts, and inspected her records, the technique of induction is shown in detail, using pure N₂O. When this stage is reached oxygen is introduced, and then ether is added to the circuit cautiously. The effect of introducing ether rapidly is shown, and the method of controlling the resulting coughing or laryngeal spasm. Main-

tenance of surgical anaesthesia is demonstrated. Next, the film shows by diagram the gas flow in a partial rebreathing circuit the effects of CO₂ accumulation, the results of increasing or reducing the total gas-volume, and the dangers of tissue ether-saturation. This film is of particular value for the student, who rarely uses the more complicated techniques, but prefers something more suited to hospital routine than open drop ether. The film presents clearly the important steps as well as simple hints, and should be of great teaching value, although it is more mechanistic than humanistic in its approach by comparison with some of the others reviewed in this issue. *B S*

851 No. 5 : Endotracheal Anaesthesia

made by Realist Film Unit, 1944, owned by ICI, 16 mm sound, 940 ft. (280 m), 35 mm sound, 3550 ft (1060 m), black and white, 39 minutes

This film deals with all aspects of endotracheal anaesthesia. As in previous films in this series, the simplest possible apparatus is selected for demonstration, and the student is even shown how to make an endotracheal catheter from a coil of rubber tubing. The hints on the care, storage and sterilization of catheters is also excellent. There is a clear demonstration of the technique of passing both oral and nasal catheters. Animated diagrams and actual photographs of the larynx help to illustrate each point and there is also a demonstration of faults in technique and their results. The film includes examples of the uses of endotracheal anaesthesia. Once again clarity of presentation and photographic excellence place this film with the others in this series in the first rank of medical teaching films. *A F-C*

852 No. 10 Operative Shock

made by Realist Film Unit, 1945, owned by ICI, 16 mm sound, 587 ft. [180 m], 35 mm sound, 1467 ft [440 m], black and white, 16 minutes

The film starts with a description of the physical signs of operative shock, and emphasizes the importance of detecting this condition in its early stages. This can be done by careful observation of the pulse rate and blood-pressure. The first sign of danger is usually an increasing diminution in the difference between the systolic and diastolic blood-pressure. It is pointed out that the condition of shock may be more easily prevented than cured, and the underlying causes are considered. Dehydration of the patient can be prevented by avoidance of excessive purgation and by allowing the patient to drink glucose and tea up to 2 hours before the operation. The necessity to keep the patient warm so as to avoid loss of heat is emphasized. Before a long and serious operation it is important to avoid the minor accidents of anaesthesia e.g. respiratory obstruction struggling and vomiting, and it is therefore advisable to administer an intravenous barbiturate before using ether. Traction on the mesentery during light anaesthesia and the unnecessary exposure

of viscera and large raw surfaces lead to a fall in blood pressure and encourage the development of shock. The dangers arising from prolonged deep anaesthesia and prolonged de-oxygenation of the patient can be avoided by maintaining an anaesthesia as light as is compatible with full surgical relaxation and by keeping the airway free. Sudden changes in posture e.g. from the Trendelenburg position to the horizontal are dangerous. The importance of a pre operative injection of a vaso pressor drug especially before a high spinal anaesthetic, is mentioned. The danger of a low blood-pressure is that there is little margin of safety should an accident such as haemorrhage take place.

Turning to the treatment of shock, the film emphasizes the importance of intravenous drip saline in any major cerebral abdominal, or thoracic operation. It is also advisable when a major amputation is contemplated. Once the drip saline is working it is easy to change over to a transfusion of blood or plasma, should this become necessary. A blood-pressure of 90 mm systolic is given as the danger point at which intravenous drip saline must be started at a rate of 60 drops per minute. This figure increases as the blood-pressure falls until 120 drops a minute may be necessary if the systolic blood-pressure has fallen to 60. When shock has already developed it is advisable to stop the operation until the drip saline is started, and if a response is not speedily observed it will be necessary to advise the surgeon to cease his work altogether.

This useful film will find a place in the teaching of anaesthetics though it is probable it will be of more value to the post graduate students than to the undergraduate. Even for the latter however it will have importance for it will show that one more of the major complications of anaesthesia is explainable and treatable. *A*

853 No. 11 : Handling and Care of the Patient

made by Realist Film Unit, 1945, owned by ICI, 16 mm sound, 940 ft. [280 m], 35 mm sound, 2340 ft [700 m], black and white, 26 minutes

How to reassure the patient undergoing an anaesthetic and how to look after him until he regains consciousness. This film contains a wealth of information, and must be seen many times to be fully appreciated. It is in two parts, the first itemizing all the simple errors which can impair the smooth course of anaesthesia and make it an ordeal to the patient, indifference of attendants, unnecessary noise faulty apparatus—all are shown and once seen can be guarded against in the future. The second part shows the course of an ideal anaesthesia: the patient is reassured in many little ways and falls peacefully asleep. The method of positioning a patient on the table, the need for maintaining warmth care of the eyes, and maintenance of a free airway are shown with a few unusual causes of embarrassment such as leaning on the chest or retracting the liver unnecessarily hard. The safeguards to be observed while taking the patient back to the ward are followed by details of necessary attention until consciousness returns, the prevention of inhalation of blood or vomit being given special attention. This is an excellent film which shows the importance of treating a patient as a person and not as a 'case'. It will be widely appreciated by nurses as well as students, theatre porters and anaesthetists. *B S*

BOOKS

ENDOCRINOLOGY

854 Biological Actions of Sex Hormones 612.6

Harold BARRON. CAMBRIDGE UNIVERSITY PRESS 1945 x + 514 PAGES. 25 x 17 cm. £2 2s. [£2 1]

(i) The nature and functions of gonadotrophins (ii) factors which influence the gonadotrophic activity of the pituitary (iii) factors which influence the reaction of the gonads to gonadotrophins (iv) factors which affect the cytological

structure and weight of the anterior lobe of the pituitary (v) a general view of the gonadal hormones (vi) androgens (vii) the action of androgen on the reproductive organs before their complete differentiation (viii) the action of androgen on the reproductive organs after their complete differentiation (ix) the action of androgen on the accessory generative organs (x) the action of androgen on tissues and organs other than those already dealt with (xi) oestrogens (xii) the action of oestrogen on the embryonic gonads and Mullerian and Wolffian systems (xiii) the action of oestrogen on the anterior lobe of the pituitary and on the gonads after their differentiation (xiv) the action of oestrogen on the accessory genital organs after their differentiation (xv) a special reference to uterine hernia (xvi) the effects of oestrogen on the mamma (xvii) factors in the causation of mammary cancer (xviii) the effects of oestrogen on connective tissues and skin (xix) the actions of oestrogen on cells other than those considered in earlier chapters (xx) the actions of oestrogen on the hormones of the adrenal cortex Appendix abbreviations Glossary References. Glossary Index.

It is almost twenty years since oestrone was first isolated in the crystalline state. Since that exciting time extensive chemical studies have resulted in the determination of the chemical structures of the oestrogens, androgens and progesterone, the partial synthesis of steroid sex hormones, the discovery of the synthetic oestrogens and the total synthesis of a naturally-occurring oestrogen. Conditions have thus for some years been favourable for exhaustive and definitive studies of the biological properties of the pure hormones made available by the skill of the organic chemist. The rapid opening up of this field has naturally stimulated chemical and biological studies of the trophic sex hormones of the anterior pituitary and body fluids, which, because of their protein nature, present a harder problem to the chemist and perhaps for that very reason challenge a multiplicity of biological studies. As a result of all this research activity during the years immediately preceding the war, we may expect now that peace has been restored, something in the nature of a steady flow of monographs and treatises dealing with this branch of endocrinology. The first to appear is the present book by Dr Burrows.

The scope and complexity of science is now such that it is virtually impossible for one man to venture authoritatively, at any level higher than a student's text, outside his own specialized branch of any given field, hence this is the era of the co-operative treatise. Dr Burrows is therefore to be commended for his courage, if not for his discretion, in attempting for his task which nowadays would appal anyone but an Aberhalden or an Oppenheimer. Until a new "International Standard" becomes available, any book attempting to deal in detail with the sex hormones must stand comparison with Allen's *Sex and internal secretions*, in which each aspect of the subject was entrusted to a specialist of acknowledged standing. It must be said that judged by this standard much of Dr Burrows' book fails to convey to the reader that sense of authority which he has the right to expect in a work of this nature. Facts in plenty there are, but one often feels that the best selection has not been made and the authoritative interpretation so necessary to guide the reader through the complications of modern sex endocrinology is mostly lacking. This does not, of course, apply to the section dealing with cancer, on which Dr Burrows is a well-known expert.

In reading the book one is forcibly reminded of the prevailing sad state of confusion as regards much of the terminology in use in this field at the present time. Here is evident a lamentable lack of international co-operation which might well be taken in hand by Unesco. Dr Burrows is to be commended for eschewing the truly hideous Greek terms recently introduced by Van Dyke in respect of the pituitary gonadotrophins, but he would have been well advised not to add to the existing chaos by replacing the temporarily convenient "F S H" by a modification of his own. The way he uses the existing terms "mammothrophin" and "prolactin" and his new term "galactogen" is more likely to confuse the non-specialist reader than to enlighten him. Moreover, there seems to be little justification for using obsolete terms like "oestrin" and "progestin" more or less interchangeably with their modern equivalents, nor for vacillating between "oestrus" and "oestrum" and between "oestrous" and "oestral". Reproductive physiologists will be joined by the feminine half of the human race in protest at his use on page 328 of the adjective "oestrous" in respect of the ovarian cycle in woman.

When these criticisms have been made it can be said that Dr Burrows has nevertheless accomplished something of a feat in compiling such a considerable digest of a not readily digestible literature. Even the sophisticated endocrinologist will find it a useful source of well-documented information, though the quoted experiments are often described in unnecessary detail—for instance, it would have been better from many points of view to draw the veil of discretion over the macabre details of one of the experiments described on page 53. Specialists are quite likely to find a few references, dealing with their own particular branches, which are new to them. The complete absence of illustrations is perhaps surprising in a book of this nature, and of the glossary it may be said that it should have been made comprehensive or omitted altogether. One entry is frankly misleading, it describes pitocin as a pressor hormone, whereas this preparation is primarily standardized for oxytocic activity.

DENTAL SURGERY

855

Acrylic Resins in Dentistry

John Osborne SECOND EDITION OXFORD BLACKWELL SCIENTIFIC PUBLICATIONS LTD 1945 vii + 144 PAGES 81 ILLUSTRATIONS 22 x 14 cm 12s 6d [£0 62s]

(i) History of plastics in dentistry (ii) composition and manufacture of acrylic resins, (iii) properties of acrylic resins (v) manipulation models, waxing up, flasks, flaking, mixing applying separating media, packing deflasking filing and polishing, (vi) repairs cracked teeth, (vii) acrylic teeth (ix) all acrylic immediate dentures (x) acrylic inlays, crowns, and bridges, (xi) other acrylic prostheses Appendices Index

To those unfamiliar with wartime developments in the use of plastics for dental purposes, this book will serve a useful purpose. The first chapter briefly reviews the materials that were introduced in the period 1924-44, but subsequent chapters deal solely with the so-called acrylic resins—the polymerized form of methyl methacrylate. The composition, manufacture and properties of the resin are dealt with.

A useful comparison is made of existing commercial acrylic resins with dental rubbers from the laboratory standpoint but as was well shown with the earlier vinyl resins, laboratory evidence alone is apt to be inconclusive. The author, for example, states that processing resins in the vulcanizer under pressure softens them considerably, but clinical evidence does not support this contention.

In the chapters on manipulation, the usual flasking procedures are dealt with, followed by the preparation of the acrylic dough, use of separator and packing the dough. The suggestion of using tin filings for weighting lower dentures would seem ill-advised, because of the risk of drift to the outer surface of the denture, during closure and curing. As the author says, weight alone will never solve the problem of lower-denture stability.

The reader will find sound comment on the two common problems of raised bite and cracked teeth. A chapter on acrylic teeth discusses the subject with adequate detail and is followed by one on all-acrylic immediate dentures. A short paragraph at the end of the latter chapter on relining fails to comment upon the wide use in America and to a lesser extent in Great Britain of an immediate relining technique employing a partially polymerized mass of acrylic resin in the denture as the impression material. These self-hardening lining materials have been the subject of very critical comments by American investigators. A chapter on acrylic inlays, crowns and bridges follows, and the last chapter deals with other acrylic prostheses. Here the author's comment is in part uncritical, and to that extent one is left in some doubt as to the actual extent of his experience.

THERAPEUTICS

856

ABC of Medical Treatment

E Noble Chamberlain LONDON HUMPHREY MILFORD OXFORD UNIVERSITY PRESS 1946 viii + 206 PAGES 19 x 12 cm 10s 6d [£0 52s]

The purpose of this small book is to provide a brief account of the treatment of the more common medical ailments. Surgical, gynaecological, dermatological and other specialized subjects have been excluded. The subject matter has been arranged in alphabetical order for ease of reference and a number of symptoms (e.g. pain, insomnia) have been included to avoid repetition in dealing with the individual diseases.

The book is primarily intended for the general practitioner who wishes to make a quick reference to the essentials of treatment, and more space has therefore been devoted to the illnesses commonly dealt with in general practice. No attempt has been made to include measures of treatment which are not of generally accepted value. An essential feature of the book is the inclusion of diet sheets, constructed by Miss Rose Simmonds, from which a selection has been made and incorporated with the general text, in which the suitable diet is merely referred to by its number.

MEDICINE AND MAMMON

857

Guide to Medical Practices

Ramsay Brown LONDON H K LEWIS & CO LTD 1946 56 PAGES 16.5 x 10.5 cm 2s [£0 2s]

(i) Introduction, (ii) practice (iii) house (iv) purchase price (v) finance (vi) vendors accounts, (vii) budget (viii) introductory period (ix) special sources of income (x) accounts (xi) income tax (xii) panel (xiii) d-t.

NEW EDITIONS

616(02)

860 A Textbook of the Practice of Medicine

Frederick W Price SEVENTH EDITION LONDON OXFORD
UNIVERSITY PRESS 1946 xiv + 2034 PAGES 91 ILLUSTRATIONS.
22 x 14 cm. £2 2s. [£2 1]

(i) Infection, immunity the filtrable viruses bacteriophage penicillin
(ii) general infectious diseases (iii) diseases due to metazoa (iv) diseases due
to physical and chemical agents (v) diseases of metabolism (vi) deficiency
diseases, (vii) diseases of the endocrine glands (viii) diseases of the digestive
system (ix) diseases of the blood (x) diseases of the spleen and the reticulo-
endothelial system (xi) diseases of the lymphatic system (xii) diseases of the
circulatory system (xiii) vasomotor neuroses (angio-neuroses) (xiv) diseases
of the respiratory system (xv) diseases of the kidneys (xvi) diseases of the
joints and inflammatory diseases of the fibrous tissues and muscles (xvii)
diseases of the skeleton (xviii) diseases of the skin (xix) diseases of the nervous
system (xx) psychological medicine

Affectionately known as the "student's bible," this work has come to be recognized as the standard English textbook of medicine. Drawing his contributors from the London teaching hospitals, the editor has produced a book that can justly claim to be representative of the best traditions of the London school of medicine. The death of Sir Arthur Hurst deprived the book of one of its most outstanding contributors, but fortunately he had revised the greater part of his section before his death. The process of revision has been completed by Professor L J Witts. The only other change in personnel is in the section on neurology, which for this edition has been revised by Dr Purdon Martin and Dr J St C Elkington, who thus maintain the close association of this section with the National Hospital for Nervous Diseases.

While London has every reason to be proud of this work, there is no room for complacency. As our American colleagues are so fond of pointing out, "time marches on," and if this book is to maintain its position in the medical hierarchy, much more care must be devoted to the preparation of the next edition. In view of the difficulties under which the present edition has been produced, the editor and his contributors are deserving of congratulation, but they must realize that no one can afford to rest on his laurels. In the first place, they must decide whether they are writing a textbook or an encyclopaedia. Too often is the difficult process of selection replaced by a mere catalogue of diseases, some of which have no place at all in a textbook of medicine, for instance, the section on diseases of the blood-vessels contains subsections on such entirely pathological entities as diffuse hyperplastic sclerosis, Monckeberg's medial sclerosis, and fatty degeneration of the media. Even to suggest that these are clinical entities that have special symptoms, a definite prognosis and a definite form of treatment is merely intellectual obscurantism.

The question of what specialties should be incorporated in such a textbook as this also requires careful thought. Many, for instance, would feel that there is no good reason for including a special section on dermatology, and that the space devoted to this might be more profitably employed. There are so many first-class textbooks of dermatology that such a section in a textbook of medicine is redundant. One of the great defects of this book has always been the absence of adequate illustrations. It has been well said that one good illustration is worth a page of script, and in these days when the educational value of the graphic art is being increasingly emphasized, it is disappointing to find so little if any, advance in this respect in the present edition.

Finally—and this is a fault that appears to be inherent in textbooks as a *genus*—the old and discarded has not been pruned sufficiently. It is distressing, for instance, to find pulv. jalp. co still recommended in the initial treatment of acute nephritis, while calomel is still included in the treatment of pneumonia. A similar reluctance to depart from the old purging habits is also shown in the treatment of diabetes mellitus. While recent advances are not to be expected in a textbook it is with a shock that the reader finds sulphapyridine recommended as the drug of choice in the treatment of lobar pneumonia. Similarly no mention is made of the sulphonamides in the prevention of rheumatic fever. Indeed prophylaxis in this disease is dismissed with a reference to tonsillectomy and appendicectomy. Again care must be taken in a standard textbook to avoid discarding

This book, the title of which is somewhat cryptic if not misleading, deals with the business side of medical practice. Its author is a chartered accountant who has had considerable experience in investigating general medical practice from the financial point of view. Apart from purely financial questions, the book deals briefly with the advantages and disadvantages of different types of practice, with professional etiquette and with various problems which confront the beginner. The advice given is sound enough in the main, but the author is not always on sure ground and some of his statements are more amusing than instructive. In the chapter on "Special sources of income" we are told that "Since King Edward VII had his appendix out appendicectomy has been fashionable and in certain cases necessary," and that "circumcision is a small operation carried out both among Jews and Gentiles, which is quite remunerative." The chapters on accounts and on income tax are clear but very brief, and these sections, in which the author writes as one having authority, could well have been expanded. The author himself states that it might have been advisable to defer the writing of this book until the Government proposals for the National Health Service have matured. At the time of going to press it seems certain that private medical practice will be considerably affected and that all or much of this book will be outmoded.

NURSING

858 Aids to Orthopaedics for Nurses 617 3

Bertha E Waller LONDON BAILLIERE, TINDALL AND COX, 1945
213 PAGES 97 ILLUSTRATIONS 16.5 x 10.5 cm. 4s. [£0-2]

(i) Introduction (joints splints measurements required for the instrument maker), (ii) diseases of the nervous system, (iii) tuberculosis of bones and joints (iv) congenital and acquired deformities (v) rickets, (vi) diseases of bones and joints, (vii) injuries to bones and joints (viii) physiotherapy (ix) plaster technique

This addition to the *Nurses' Aids* series covers the syllabus for the final orthopaedic examination of the General Nursing Council and provides a concise textbook for the student engaged in orthopaedic nursing. The book will also serve as a useful work of reference for the general nurse. Miss Margaret Dolesio contributes a chapter on physiotherapy, and there are appendices dealing with the iron lung, with the preparation of patients for operation, and with operating theatre technique. There is also a glossary of terms in common use in orthopaedic surgery. There are a few misspellings of personal names, such as Bohler (Bohler) and Lambrinudi (Lambrinudi), the name of Denis Browne is given correctly in the text but is entered under Dennis in the index, the index refers to Bankhart's wedge, page 111, but the correct reference is 112, where the name is correctly spelt Bankart. In the section on torticollis (page 176) affected "should be effected." These are minor blemishes in a worthy addition to this useful series. The author is sister tutor at the Royal National Orthopaedic Hospital and examiner to the General Nursing Council and other bodies.

MEDICAL HISTORY

859 Ancient Anodynes. Primitive anaesthesia and allied conditions 617-089 5(09)

E S Ellis LONDON WILLIAM HEINEMANN (MEDICAL BOOKS)
LTD 1946 187 PAGES. 22 x 14 cm. £1 1s. [£1 05]

(i) Introductory (ii) anaesthesia by physical means (iii) psychological anaesthesia (iv) inhalation (v) anaesthesia by known drugs, (vi) unnamed and various drugs (vii) local anaesthesia (viii) anaesthesia in different countries (ix) modern anaesthesia (x) conclusion References. Index.
[See BMB 846 for review.]

treatment simply because something newer has been introduced, but there is no excuse for sentences such as this "Novasurol is by far the most toxic of this group of diuretics, and its use has been abandoned in favour of other preparations which are safer and little if at all inferior in potency." Then, why mention it at all?

These criticisms must not be taken as detracting from the value of the book. Rather are they evidence of the respect in which it is held by the reviewer, in that he has considered it worth while to give such a detailed criticism. As a guide to the practice of medicine, this work can be safely commended to both student and practitioner. The detailed index occupies 100 pages of the book, and is a necessary appendix to a volume containing so great an amount of varied information.

861 A Manual of Tuberculosis: Clinical and Administrative

E Ashworth Underwood THIRD EDITION EDINBURGH, E & S LIVINGSTONE LTD 1945 xvi + 524 PAGES, 88 ILLUSTRATIONS 18 x 13 cm 15s [£0 75]

(i) The seed, the soil and the sowing (i) the reaction of the body, (ii) the evolution of pulmonary tuberculosis (iv) allergy and immunity in tuberculosis (v) pulmonary tuberculosis—symptoms and signs (vi) x rays and their use in tuberculosis, (vii) the course and complications of pulmonary tuberculosis, (viii) the institutional treatment of pulmonary tuberculosis (ix) management of patients in institutional treatment, (x) the mental aspects in tuberculosis, (xi) the medical treatment of pulmonary tuberculosis, (xii) collapse therapy, operative methods in diagnosis and treatment (xiii) tuberculosis in children, (xiv) tuberculosis of bones and joints, (xv) light treatment in tuberculosis (xvi) laboratory methods, (xvii) the domiciliary management of tuberculosis, (xviii) disinfection and disinfectants (xix) the post sanatorium régime instructions to the patient, (xx) the tuberculosis dispensary, (xxi) administrative measures, (xxii) the epidemiology of tuberculosis, (xxiii) tuberculosis and social medicine (xxiv) tuberculosis and war Glossary Recommendations for further study Index

There are not many books of recent date in English on tuberculosis, and such works as do exist are practically all confined to the pulmonary or the non-pulmonary forms of the disease, or to particular problems of administration and control. The treatment of any case of tuberculosis nearly always demands action which is far beyond the scope which the older physicians would have considered as falling within their province, and any doctor who has to deal with such a patient should certainly know sufficient about the modern non-medical methods to enable him to guide the patient under the supervision of the expert. It is strange that up to the present neither the student nor the junior physician—in hospital or in general practice—could turn to any single book with the feeling that in it he would be able to obtain an introduction to the whole of the tuberculosis problem, whether on the pathological, the clinical, the social, or the administrative aspects.

Dr Ashworth Underwood has now filled the breach in an eminently satisfactory manner. In the third edition of his well-known *Manual*, he has rewritten the book almost entirely with this end in view—namely, to present a comprehensive account of tuberculosis in all its aspects, clinical, social and administrative. In this task he has been entirely successful, and he has provided a textbook which is unique in its scope and in the manner of its presentation. Despite the wide field which is covered, the book is written in a simple and clear style which carries the reader along without effort, and, although Dr Underwood writes essentially for the student and practitioner, there is no reason why the work should not be of great value to lay administrators and nurses who are specializing in tuberculosis work.

After introductory chapters dealing with the tubercle bacillus, methods of infection, and pathological features, there are new chapters on the evolution of pulmonary tuberculosis, on allergy and immunity, on x rays and their uses, and on the mental aspects of tuberculosis. The clinical aspects of pulmonary and non-pulmonary tuberculosis are dealt with in an attractive manner, and later in the book there are other new chapters on clinical laboratory methods, on tuberculosis and social medicine, and on tuberculosis and war. The sections on after-care and rehabilitation, on administrative measures, and on epidemiology are especially good, and there is a masterly exposition of the application of maintenance allowances. A glossary of technical terms, though intended for lay tuberculosis workers, may be studied with profit by others. There is a well-selected bibliography and a full index.

The general production of the book does justice to the high standard of its contents. The illustrations, particularly the radiographs, are excellent. Dr Underwood has produced a book which is a model of its kind, and which ought to be read by everyone engaged in tuberculosis work. Though it is essentially an exposition of British practice, due note is made of important researches in other countries.

862 Medical Jurisprudence and Toxicology 340 6

John Glaister EIGHTH EDITION EDINBURGH E & S LIVINGSTONE LTD, 1945 xii + 691 PAGES, 222 ILLUSTRATIONS (89 IN COLOUR) 22 x 14 cm. £1 10s [£1 5]

(i) General Medical Council, malpraxis legal procedure, and workmen's compensation, (ii) medical evidence, (iii) identification (iv) the medico-legal aspects of death, (v) death certification and cremation, (vi) asphyxia, (vii) death from lightning, electricity and burning, (viii) death from starvation and neglect and from cold and exposure effects of heat, (ix) wounds (x) examination of blood, (xi) states of legal aspects of sexual functions and criminal abortion murder, (xiv) rape and carnal knowledge and other sexual crimes, (xv) lunacy in its medico-legal aspects, (xvi) law relating to poisons (xvii) general action of poisons evidence and treatment of poisoning, (xviii) corrosive poisons, (xix) metallic and some non-metallic poisons, (xx) gaseous and certain volatile poisons and anaesthetics, (xxi) the alcohols, (xxii) hypnotics and anupretics (xxiii) vegetable poisons, (xxiv) additional poisons (xxv) food poisoning (xxvi) plant irritants, arrow poisons stings and bites (xxvii) war gases and effects of blast Appendix Index

Glaister's *Medical jurisprudence and toxicology* has long been established as one of the standard works on its subject, and this new edition, which has been fully revised and brought up-to-date, will maintain its reputation. Considerable additions have been made to the text, particularly on the more purely legal side. The sections on identification are extremely detailed and give much information unobtainable in any other book intended primarily for the doctor. The number of illustrations has been greatly increased, but the colour photographs, which are introduced for the first time, leave room for improvement. In this edition the names of authors have been added to the references at the ends of the chapters, but it would make for even greater ease of reference if these lists were arranged according to one of the more modern systems in which the authors' names are given first place in the entry.

863 A Synopsis of Forensic Medicine and Toxicology

E W Caryl Thomas SECOND EDITION BRISTOL, JOHN WRIGHT AND SONS LTD 1945 viii + 179 PAGES 18 5 x 12 cm 10s [£0 5]

(i) Legal position and responsibilities of the medical man (ii) medical evidence, (iii) signs of death and phenomena which follow death (iv) medico-legal aspect of identification, examination of the dead, exhumation and embalming (v) modes of dying (vi) death from special causes (viii) examination and recognition of blood stains, (ix) sexual matters and pregnancy (x) abortion birth infanticide, stillbirth, (xi) insanity, mental deficiency drunkenness in its legal relations, (xii) insurance (xiii) toxicology, (xiv) corrosive and irritant poisons (xv) narcotic and other poisons

In this synopsis the extensive subjects of forensic medicine and toxicology have been considered from the point of view of the general medical practitioner, but the book is extraordinarily complete and is a marvel of compression.

864 Diagnosis and Treatment of Diseases in the Tropics

H C Tronell SECOND EDITION LONDON, BAILLIERE TINDALL & COY 1945 xiv + 219 PAGES 35 ILLUSTRATIONS 16 5 x 10 5 cm 4s [£0 2]

(i) The general principles of medical diseases, (ii) the common signs of medical diseases (iii) the general principles of surgical diseases, (iv) common surgical diseases, (v) special varieties of inflammation, (vi) special surgical diseases, (vii) general fevers (viii) fever due to local inflammation (ix) diseases of the digestive tract, (x) special medical diseases, (xi) venereal and other special diseases (xii) diets and malnutrition Index

This little book is one of the series of *Medical manuals for Africans* and is written for the instruction of native nurses, dispensers and health orderlies. The author has had considerable experience of practice and teaching in Kenya and Uganda and he has succeeded in his avowed aim of conveying what he considers to be the basic knowledge of medicine and surgery which must be acquired in order for nursing to become intelligent. In this edition, which contains a new chapter on Diets and

Nutrition, the book is admirably designed to serve the purpose for which it was written

616 8 (02)

865 Diseases of the Nervous System Described for Practitioners and Students

F M R *Walke* FOURTH EDITION EDINBURGH E. & S LIVINGSTONE LTD 1945 xvi + 360 PAGES 51 ILLUSTRATIONS 22 x 14 cm. 15s. [£0 75]

(i) Introduction non anatomical factors in diagnosis (ii) anatomical or localizing factors in diagnosis (iii) space-occupying lesions within the skull tumour haematoma, abscess (iv) vascular disorders of the brain (v) epilepsy idiopathic and symptomatic (vi) migraine (paroxysmal headache) (vii) acute infections of the nervous system (viii) syphilis of the nervous system (ix) disseminated sclerosis (multiple sclerosis) (x) paralysis agitans (Parkinson's disease) (xi) rheumatic chorea (Sydenham's chorea) (xii) injuries of the brain concussion and contusion (xiii) compression and injuries to the spinal cord (xiv) subacute combined degeneration of the spinal cord (xv) the heredo-familial ataxias (xvi) Friedreich's disease (xvii) muscular atrophies (xviii) myasthenia gravis (xix) multiple peripheral neuritis (polyneuritis) (xx) lead poisoning of the nervous system (xxi) common affections of the cranial nerves (xxii) sciatica and brachial neuritis (xxiii) affections of the spinal nerves (xxiv) some common nervous affections of infancy and childhood (xxv) bromide intoxication (xxvi) some general observations upon the treatment of nervous diseases (xxvii) torticollis and the tics (xxviii) occupational cramps (xxviii) the psychoneuroses, (xxix) a simple scheme of examination of the nervous system Index

The fact that this book has reached a fourth edition within five years of its first publication is sufficient indication of its value as an introduction to clinical neurology. It is a thoroughly practical textbook based upon the author's long experience in practice and teaching and its success is well deserved. In this edition the chapters on peripheral nerve lesions, herpes zoster, cervical rib, sciatica and protrusion of the intervertebral disc have been rewritten, and new sections on the aetiology of nervous disorders and on psychosomatic illness have been included. The radiograms and other illustrations are excellent, but there are several errors in the references to them in the text

In one or two cases the page references in the index have not been correctly altered in conformity with the revised text, and Frohlich's syndrome has been entered as Frolich's " syndrome (For review of previous edition see BMB 344/12)

866 Surgical Nursing and After-Treatment 617-083

H C *Rutherford Darling* NINTH EDITION LONDON J & A CHURCHILL LTD 1946 viii + 694 PAGES 211 ILLUSTRATIONS 18 x 12 cm. 12s. 6d. [£0 625]

Section I General Surgical Nursing (i) Bacteriology infection, inflammation suppuration and rigors (ii) immunity and new growths (iii) septic infection—local general and regional (iv) ulceration, bedsores and gangrene (v) tetanus, gonorrhoea and syphilis (vi) tuberculosis anthrax snake-bite and burns and scalds (vii) wounds—varieties complications and treatment (viii) surgical technique (ix) ligatures surgical needles lotions powders and drainage materials (x) the operating theatre (xi) operations in private practice (xii) instruments required for surgical operations (xiii) after treatment of operations, immediate and remote (xiv) haemorrhage (xv) shock, syncope, collapse concussion and cerebral irritation (xvi) splints castings and extension apparatus (xvii) fractures dislocations and sprains (xviii) surgical nursing operations (xix) bandaging—principles of bandaging, special bandages—slings Section II Regional Surgical Nursing (xx) operations on the head (xxi) tracheotomy intubation, asphyxia and drowning (xxii) neck and chest operations (xxiii) operations on the abdomen (xxiv) operations on the stomach and intestines (xxv) operations on the biliary passages appendix and hernia (xxvi) operations on the rectum (xxvii) the urine (xxviii) genito-urinary operations (xxix) gynaecological operations (xxx) eye operations (xxxi) ear nose and throat operations (xxxii) affections of the spine (xxxiii) operations on the extremities (xxxiv) massage and movements (xxxv) operations on diabetic patients (xxxvi) collection of pathological specimens (xxxvii) preparation for radiological examination and radium therapy Appendix.

This valuable textbook and reference book has already proved its worth not only to members of the nursing profession but also to medical students concerned with the care of patients in the surgical ward. The ninth edition has been thoroughly revised and brought up to date, and includes a number of practical suggestions born of the author's own recent experiences as a surgical patient.

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CORRIGENDA

Vol 3, No 6

- BMB 726/1, para 4 for Davy had (in 1799) discovered nitrous oxide, read Davy had (in 1799) discovered the anaesthetic property of nitrous oxide
BMB 728/1, line 7 for valves read valves

Vol 3, No 9-10

- BMB 794/18 In the review of *Tratamiento pre y postoperatorio*, for proteinaemia read hypoproteinaemia

Vol 4, No 1

In vol 4, no 1 of the Bulletin several misplacings of type occurred, especially on page 1, after the page proofs had been passed for press. Among such misprints, the following should be noted

- | | |
|---|---|
| Page 13, col 2, line 33 for alpha radiation read alpha radiation ⁸ | Page 20, col 2, line 15 for Muller-read Muller, |
| Page 16, col 1, line 7 for 400 ions read 400 ions/μ | Page 41, col 2, line 8 for FI2 12 read FIG 12 |
| Page 20, col 2, line 12 for hemi, read hemi- | Page 41, col 2, line 11 for Mihler read Miller |
| | Page 74, col 1, line 1 for 81 read 815 |

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Congenital Factors in Disease

CONGENITAL FACTORS IN DISEASE has been chosen as a descriptive title for this number, although it is realized that there are certain objections to the use of the term 'congenital'. As Professor Crew points out, 'congenital' has no etiological significance, but refers simply to a point in time. Nevertheless, the term has its convenience as an indication of defects determined before birth—whether genetically, environmentally (as an effect of maternal disease during pregnancy), or as a genetically-determined environmental incompatibility (as in erythroblastosis foetalis).

PROFESSOR F A E CREW was for many years director of the Institute of Animal Genetics, University of Edinburgh. During the recent war he was appointed as director of medical research, and later as director of biological research, to the War Office. More recently, he was appointed to the Bruce and John Usher chair of public health in the University of Edinburgh. With his translation to the chair he now holds, its title has become changed to indicate its enlarged scope and is now the chair of public health and social medicine. He is the author of *Animal genetics* (1925), *Organic inheritance in man* (1927), *Sex determination* (1933) and of numerous other publications dealing with these and related matters. In the dual capacity of physician and geneticist, Professor Crew speaks with unusual authority on those wider aspects of medicine in which inheritance plays an important part, and his article in this number provides a characteristically stimulating introduction to the subject.

DR B WOOLF who contributes the second article in this number, is lecturer in medical statistics in the University of Edinburgh where he is building a statistical research unit willing to assist and co-operate with all medical and social agencies in Scotland in research projects in the field of social medicine. He has made a detailed statistical study of the relation between social conditions and infant mortality, of which part 1 has been published (*J Hyg, Camb* 1945, 44, 67) and part 2 is to appear in the new *British Journal of Social Medicine*, which is to be published by the British Medical Association under the joint editorship of Professors F A E Crew, Lancelot Hogben (who has such diverse achievements to his credit as the authorship of *Mathematics for the million* and of the *Xenopus laevis* test for pregnancy), and J A Ryle. Dr Woolf began his research career as a biochemist under Sir Frederick Gowland Hopkins at Cambridge, and has published papers on bacterial metabolism, enzyme action, the chemistry of immunity, and other topics. Becoming increasingly interested in the social aspect of medical problems he acquired a knowledge of modern statistical theory and practical computational methods and accepted an invitation from Professor Lancelot Hogben to come to Birmingham University to lecture and research on social biology. During the war he was engaged for a time on medical statistical research at the War Office.

DR AGNES R MACGREGOR is lecturer on pathology of diseases of children in the University of Edinburgh, pathologist and bacteriologist to the Royal Hospital for Sick Children, Edinburgh and pathologist for infants to the Edinburgh Royal Infirmary. She was formerly a lecturer on pathology and bacteriology in the School of Medicine of the Royal Colleges, Edinburgh. For some years Dr Macgregor has made a special study of neonatal pathology and her published work includes papers on this subject, as well as on pneumonia and tuberculosis in childhood. For two years during the war she was a member of a team engaged in an inquiry on behalf of the Medical Research Council into the incidence of tuberculosis due to human and bovine type tubercle bacilli throughout Scotland.

DR H S BAAR holds the degrees of M D and Ph D of Vienna, and was for 20 years on the staff of the St Anna Children's Hospital in that city. In December 1938 he was appointed research Fellow at the Children's Hospital, Birmingham, where he subsequently became research pathologist.

Dr Baar has published a book on haematology in childhood, a monograph on alimentary anaemias, and over fifty scientific papers. At present he is engaged in work on the pathology of an infective encephalitis of the newborn transmissible to animals, and in the preparation of a paper on the pathology of fibrocystic disease of the pancreas—upon which a preliminary communication was read before the Association of Clinical Pathologists in January 1944.

DR R R RACE is well known as the leading British worker on the genetics of human blood-groups. He has previously contributed to this Bulletin a review of knowledge of human blood groups (with G L Taylor, *BMB* 420) and a note on their inheritance (*BMB* 421).

SIR LEONARD G PARSONS is dean of the faculty of medicine and professor of children's diseases at Birmingham University. He is one of Britain's most distinguished paediatricians and was President of the British Paediatric Association in 1942-44. He has made important contributions to the literature of paediatrics. News of the knighthood just conferred upon him reached us as we were going to press.

DR A ST G HUGGETT is physiologist to St Mary's Hospital Medical School, and professor of physiology in the University of London. He was a pupil of the late Professor John Mellanby, F R S, and of Dr John Fairbairn at St Thomas's Hospital. He inherited from Professor Mellanby an interest in the coagulation of the blood which led to work on the dyestuff anticoagulants including chlorazol pink. He has been responsible for initiating the experimental approach to foetal physiology of the last twenty years, on which subject he has published many papers.

PROFESSOR A SORSBY is the first holder of the research chair in ophthalmology which was in 1943 jointly established by the Royal College of Surgeons and the Royal Eye Hospital, London. A note on Professor Sorsby appeared in volume I of this Bulletin, to which he contributed an article on 'The task of ophthalmological research' (*BMB* 160).

DR G M BONSER is Brotherton Fellow in cancer research in the University of Leeds and pathologist to the Searcft Laboratory of the Emergency Medical Service. She has been engaged in cancer research for twenty years, working first on intrathoracic cancer and later on the hormonal and genetic aspects of mammary and testicular cancer. She has established a strain of mice particularly susceptible to carcinogens applied to the skin. Her publications include papers on 'The incidence of intrathoracic cancer in Great Britain with special reference to Leeds' (*Acta, Union internat contre Cancer* 1938, 3, 119), 'The hereditary factor in induced skin tumours in mice: establishment of a strain specially sensitive to carcinogenic agents applied to the skin' (*J Path Bact* 1938, 46, 581), 'A microscopical study of the evolution of mouse mammary cancer: the effect of the milk factor and a comparison with the human disease' (*J Path Bact* 1945 57, 413).

PROFESSOR L S PENROSE studied psychology at Cambridge and also graduated there in medicine. His work has been concerned with the influence of heredity on diseases and especially with the genetics of mental conditions. He has written many papers on mongolism, phenylketonuria, statistical analysis of the effects of shock therapy in psychosis, etc., and a standard book *Mental defect*. He has also assisted in devising intelligence tests which have been widely used in the British and Canadian armies. For some years his researches into the causation of mental defect were carried out in co-operation with the Medical Research Council at the Royal Eastern Counties Institution, Colchester. Before his appointment to the Galton Chair of Eugenics at University College London he was Director of Psychiatric Research for the Province of Ontario, Canada.

THE PLACE OF GENETICS IN CLINICAL MEDICINE

F A E CREW, M D , F R S

Usher Institute, University of Edinburgh

Introductory

It is undoubtedly the case that an understanding of genetic principles on the part of the clinician has been made more difficult by recent elaborations in genetic theory. In the text books of 35 years ago heredity was, along with syphilis, alcoholism and chronic lead poisoning, all too often the refuge of the diagnostically destitute. In the era of the unit character of Mendelism, gene—the cause, and character—the effect, were very simply and precisely related. But since then and as the result of the exceedingly rapid advances in genetic theory and methodology these earlier simplicities have given place to such complexities that genetics has failed to become that which it promised to be—an easily used instrument of precision in the hands of the diagnostician.

The term “genetic” still means that the cause of the condition being considered was present within the fertilized ovum in which the individual had its origin, having been transported thereto by the chromosomes of the nucleus of the spermatozoon, of the ovum, or of both. But it has come to mean much more than this. The cause is now a particular gene resident at a particular point along the length of a particular chromosome. Though the nature of genetic action is even yet not known, it is reasonably assumed from its effects and by analogy that it takes the form of a “chemical” impress upon the processes of development or of degeneration. This influences in a particular way the rate or direction of one or more of these processes as they shape a particular tissue(s), organ(s) or organ system(s). Thus it is that the genotype, the sum total of all the genes in the hereditary constitution of an individual, representing and delimiting all the hereditary possibilities of the individual, is the architect of its characterization, its phenotype, the sum total of its characters, its details of structure and function.

Nature Nurture as Cause

But the geneticist no longer presents the view that the gene alone is always the cause of the character. There are certain characters, for example, those of the blood-groups and of the eye-colours, which would seem to be the direct expression of particular genes unaffected in their action by any extrinsic agency. But in the fashioning of the great majority of characters, normal and abnormal, both nature and nurture, both genotype and environment, have had a hand. The gene in action is an impulse inclining development in a certain way. But the developing structures are exposed to and react to the impress of other agencies, e.g. local stimuli derived from neighbouring structures, blood-borne stimuli. They can be affected by agencies in the external world of the individual of which they are part. Save for peculiarities

such as accidental mutilation it seems probable that genotype and environmental agencies are always concerned, though not always equally, in the fashioning of any given character, and that even in instances of deficiency and infectious diseases there is a genetic difference between those who exhibit a proneness to react in such a way as to exhibit the condition and those who do not.

It is this duality in causation, the genetic inclination and the environmental provocation, that tends to make clinical genetics decidedly difficult. To disentangle the two in the case of the species which lives in an environment created by itself, and which is notable for its variety, must present considerable difficulties when the species itself reproduces so slowly, has so few offspring, fails to maintain pedigrees, and cannot be used as experimental material. It has been necessary to devise highly sophisticated mathematical techniques for the purpose. Nevertheless, it is this very fact that usually there are two causal factors very different one from the other, one being deeply hidden and protected within the constitution of the individual, the other being present in the individual's environment and therefore more or less exposed to measures of control, that has permitted medicine so frequently to disregard the genetic factor and to concentrate upon the control and prevention of the action of the environmental causes. Though the gene cannot be excised from a population save by measures of non-propagation it is often possible to prevent the provocative action of the environmental agent and thereby to nullify the action of the gene.

If, for example, in the aetiology of a condition such as tuberculosis there is a combination of a genetic proneness and an environmental provocation, the latter being a configuration of the bacillus together with a variety of unsatisfactory social conditions, then by controlling and removing the latter the former must lose all its significance. Smallpox in its most virulent form doubtless overrides all genetic differences in respect of resistance, but with lessened virulence the more resistant individuals within a population would be far less likely to succumb. During the course of several millennia it might quite well come to pass that, through the selective elimination of the relatively susceptible, a human stock would ultimately consist solely of the relatively resistant.

But it is not the way of medicine to wait upon natural selection. Through vaccination, medicine, disregarding all genetic considerations, has artificially raised (or could have raised) the resistance of all, and this in less than a hundred years. Manifestly medicine is right in thus neglecting the genetic cause in conditions of this kind. There is undoubtedly a genetic cause of Mongolism, but the gene(s) that lies at the root of this character requires a special intra-uterine environment in which to gain expression. The repair of this environment in attempts to eradicate Mongolism would seem to be a far easier task than attempts to eliminate the gene. It will probably be found that the production of many of the so-called congenital diseases as listed by the Registrar-General, congenital meaning that the abnormal characters are displayed by the newly-born, is similarly the result of the interaction of particular genotypes and peculiar agencies within the maternal environment. If this is so, then the prevention must take one of two forms, that of removing by continued selection the causal gene from the population, or that which removes or overwhelms the causal factors within the environment.

The use of the term "congenital" in connection with causation is both mistaken and misleading. It is a point in time and not a cause. It is one of a series of terms, intra-uterine (place and time), foetal (state and time), stillbirth (condition and time), congenital (really natal?), neonatal, infant (state and time), all indicating the time during the early life history of an individual when the character—genetic, acquired, and genetical-environmental in causation—is displayed. Congenital used in this sense is more inexact than many of the others since a character that is present when the child is born was, in the majority of instances, displayed by the foetus.

But we now know that not only is the gene in its action influenced, sometimes quite profoundly, by environmental agencies, we know also that the action of any one gene within the genotype can be affected equally profoundly by the action of companion genes. The genotype of a given individual includes thousands of different genes, and the genotypes of no two individuals, excepting identical twins, are alike. Each gene exerts its action amid a vast company of genes, and its stimuli are pooled with those of all the rest. Very few genes, if any, influence the development of only one character. No wonder, then, that its action may be prevented, neutralized, overwhelmed, reinforced, modified by that of certain others. In fact, it is firmly established that one and the same gene can yield quite different end-results in different genetical milieu, just as it can in different external environmental conditions. But although these facts tend to make an understanding of genetic theory more difficult, they do not prevent us from detecting gene action when it is present or from regarding a particular gene as being the prime cause of a given character.

Genetics has lost some of its attractions to the clinician during the last decade because many who yearn ardently for social betterment have derived from it certain notions that are indeed extravagant. Those who so eagerly claim that we should do for ourselves that which we have done through the application of genetical knowledge with our domesticated animals and cultivated plants, would seem to forget that those who, by manipulating the processes of organic inheritance, sexuality and reproduction, have produced the magnificent breeds and varieties, were able to construct for themselves a standard of an ideal and thus congregate in one and the same stock that constellation of characters which most closely approached this. Through the applications of genetics it is possible to do much in the fashioning of future generations, but for the existing generation genetical knowledge can do very little.

In the case of mankind we have no firm standard of the ideal constellation of human characters. In the second place it simply is not true that the major problems of civilization refer to limitations in the ability of man to control his own nature and his external world. They arise directly from imperfect co-ordination of human effort. It can perhaps be agreed that we should imitate the example of the great livestock breeders, but if we do we must give, as they gave, as much attention to the environment as to the genotype. We, like them, can begin to consider the application of genetic principles when we have created an optimum environment. It is only when such an environment has been provided that we shall know which undesirable characters, as well as desirable, are caused wholly or partly by environmental agencies, and in the production of which the genotype

is largely or mainly concerned. For the present and for a long time ahead, it is undoubtedly the case that the most rapid improvement will be secured through the control of the environmental agencies which promote health and evoke disease.

In spite of all the difficulties and of all the extravagances it is utterly reasonable to foster the growth of clinical genetics as a branch of medicine which is concerned with future generations no less than with the present. Scientific therapy, prognosis and diagnosis all must wait upon aetiology. Exactness in aetiology means precision in all the rest. One cause, and by no means an unimportant one, of abnormality is undoubtedly the gene. The recognition that gene action is involved in the production of a particular pathological character is usually based upon the distribution of that character amongst individuals related to the propositus. The family pedigree is still the main source of our knowledge of human genetics. The fact that a certain pathological condition is displayed by members of the same family is not proof, of course, that the condition is genetic in its causation, since the family is a vehicle for social as well as organic inheritance, and a purely environmental causal agent operating upon different individuals in different generations can evoke the same reaction. It is not merely the distribution of a character within a pedigree but the significant peculiarities of this distribution that indicates the action of a gene.

The Characteristic Features of Complete Dominance

- 1 The affected individual has an affected parent
- 2 The offspring of affected \times normal include affecteds and normals in approximately equal numbers. This is so because the great majority of affecteds are heterozygous.
- 3 All normals related to affected individuals are in every way normal and produce, when mated with normals, none but normals.
- 4 A single pedigree covering three generations and including both normals and affecteds is as often as not quite sufficient to reveal the genetic nature of the abnormality.

In the case of a gene that is completely dominant, to observe the transmission of the character is to witness the distribution of the gene. Examples brachydactyly, synphalangy, alkaptonuria, congenital stationary night-blindness, congenital cataract, multiple telangiectasia (Osler's disease), epiloia, keratosis follicularis (Darier's disease), Huntington's chorea. These examples are offered in order to illustrate certain points.

In the case of complete dominance it would be, if it were thought desirable, easily possible to eliminate the gene from the future population as, by the withholding of propagation from those who exhibit the character, the transmission of the gene, the presence of which is revealed by the character, would be prevented. There would seem no reason whatsoever for suggesting such action in the case of conditions such as synphalangy, since what the gene has done the surgeon's knife can repair. In the case of Huntington's chorea there is a peculiar difficulty since the average age of onset of this condition is around 35, so that an affected individual can have reproduced long before the disease displays itself. Epiloia is an example of a disease that commonly kills in infancy, only mild cases surviving to reproduce their kind. It follows therefore that mild can

beget severe, and the differences between affected parent and affected offspring must be referable to the action of modifying genes or circumstances. Since the chances that the progeny of (heterozygous) affected and normal will be affected or normal are equal, it may be thought reasonable to advise parents who have produced an abnormal child to have no others. Completely dominant genes yielding characters that are gravely disadvantageous or incompatible with continued life tend to eliminate themselves, since they destroy the individual either *in utero*, in infancy or adolescence, before that individual can reproduce. If, then, they are not infrequent in a population their prevalence must be due in part to the occurrence of fresh mutation. If in an affected individual the character is due to a mutation during the life-history of that individual, it follows that the parents of that individual would be normal.

The Characteristic Features of Complete Recessivity

1 The gene may be handed down through many generations unsuspected and unexpressed and only when two individuals, each heterozygous in respect of it, mate and reproduce, is the homozygous exhibitor of the character to be expected.

2 The vast majority of affected individuals are the offspring of parents who phenotypically are normal, but who are in fact heterozygous. Thus organic inheritance would not seem to be concerned in the aetiology of the condition.

3 Amongst the offspring of two such heterozygotes the expected ratio of normal to affected is three to one.

4 There is a familial incidence, more than one individual in a sibship being affected. The exhibition of the character is significantly more than common amongst the offspring of consanguineous marriages.

5 The offspring of affected \times normal are invariably normal, those of affected \times affected invariably affected.

6 For the recognition of gene action in such cases a single pedigree is of no value. Few pedigrees proffer full details of three generations. It is the pedigree that is pockmarked with abnormality that is recorded, one in which the abnormality is rare is seldom available, and thus it is that false impressions are so often gained. The use of a single pedigree is that it can be pooled with others of the same kind. It is to the literature on the subject that the diagnostician must turn.

Examples infantile amaurotic idiocy, alkaptonuria, albinism.

It is to be noted that the possessor of a recessive gene in the heterozygous state does not exhibit the character and cannot be distinguished from the individual in whom this particular gene is not present. It is for this reason that any attempt to eradicate the gene from a population by controlled reproduction becomes an almost impossible task. Any control of the exhibitors of the character would leave the far greater number of the heterozygous untouched. The reason why there is a greater concentration of a recessive character amongst the offspring of consanguineous marriages is that first cousins, for example, are individuals who have received in common chromosome material and therefore genes from the same pair of grandparents and that this chromosome material is therefore more likely to include the same recessive genes. If two parents produce an amaurotic idiot, for example, the odds are that one half of their offspring will possess the gene and one quarter will exhibit the character. The latter eliminate themselves, the former will survive to

carry the seed of death which they will pass on in their turn. It is reasonable, therefore, seriously to consider the desirability of advising such parents to reproduce no more.

The inclusion of alkaptonuria in this list as well as in the last introduces an interesting though somewhat puzzling phenomenon. It is clear from pedigree studies that a character such as alkaptonuria can be based on a dominant gene in certain instances, on a recessive gene in others. This observation would seem on first sight to remove all precision from genetical teaching, but this is not so. A character is the end-result of a long and intricate developmental process(es) which may be affected at quite a number of critical points during its course by the incoming of a fresh stimulus. To the character itself there must be a fairly narrow limit in the variety of its final form. There is no reason why more than one gene, although acting in different ways and at different times during development, should not lead to the same end-result. That this is so does not in the least destroy genetic theory or the clinical value of genetical knowledge.

But there is something even more difficult of acceptance than this. Dominance and recessivity are not final static properties of genes. We know that each of them can be either complete or incomplete, in fact, not uncommonly an individual who, according to the rules, should exhibit a dominant character lacks it although undoubtedly the gene is within him. The fact is, as has already been stated, that a gene in its action is exposed to and reacts to the action of many another gene in the genotype. In different gene companies this action becomes greatly altered and modified. Its penetrance, the degree or percentage of its expression as a character, can vary very greatly, being affected by the action of other genes and by that of environmental agencies.

Mutation implies a disturbance of a genotypic equilibrium. If a mutant gene behaves as a complete dominant from its very beginning this disturbance is immediate, if it is recessive its action is overwhelmed by its unmutated partner gene, and so there is no such disturbance. But if in the genotype in which a dominant mutation finds itself there happen to be genes which modify this action, its effects would be incomplete or even resemble that of a recessive. In general, it can be said that advantageous mutant genes tend to become dominant in their action, while deleterious genes tend to become recessive. This does not indicate any change in the gene itself. It merely means that in many instances a block of genes is concerned in the production of a character, the key gene being the prime agent and the rest being modifiers.

The Characteristic Features of Dominant Sex-linked (X-borne) Inheritance

1 All affected individuals have an affected parent.

2 The character is transmitted only by affected individuals and by them to approximately half their offspring.

3 Affected males \times normal females have only affected daughters and normal sons.

4 The character is twice as common amongst females as amongst males for the reason that there are twice as many X-chromosomes in the female population.

5 A single pedigree can suffice to reveal the genetic nature of the character.

6 All unaffected individuals lack the gene.

Example defective enamel of the teeth.

It will be noted that in the main the characteristic features of this type of inheritance are similar to those of ordinary

completely dominant autosomal inheritance. The two are to be distinguished by the peculiar sex-distribution as detailed in 3 and 4 above.

The Characteristic Features of Recessive Sex-linked (X-borne) Inheritance

- 1 The majority of affected individuals are males and have phenotypically normal parents
- 2 An affected female must have had an affected father and a heterozygous or affected mother
- 3 The recessive gene can be handed down unsuspected and unexpressed through one or even two generations, but it is most unlikely, unless families are exceedingly small, that it will pass through three generations without the appearance of an affected male
- 4 A single pedigree, if sufficiently large, can suffice to reveal the genetic nature of the character

Examples haemophilia, red-green colourblindness

Perhaps the most characteristic feature of the sex-linked mode of hereditary transmission is criss cross inheritance. In the case of a dominant X-borne gene, the mating of an affected father with a normal mother yields affected daughters (taking after their father) and normal sons (taking after their mother). In the case of a recessive X-borne gene, the mating of a normal father with an affected mother produces affected sons and phenotypically normal daughters.

Partial Sex-linkage

In man the Y-chromosome consists of a pairing segment which carries alleles of the genes on the corresponding portion of the X-chromosome, and a non-pairing segment which contains a few genes without such alleles. The mode of transmission of the genes on these homologous and non-homologous portions of the Y respectively is therefore significantly different.

The characteristic feature of the mode of transmission of a character whose gene is resident upon the non-homologous, non-pairing segment of the Y-chromosome, is that only males exhibit the character and each affected male transmits the character to all his sons. The gene material in this non-pairing segment is the peculiar possession of the male. The character follows the track of this segment from generation to generation.

Example webbed toes

It does not follow, of course, because a given character is restricted in its exhibition to males, either that it is genetic in origin or that its gene is Y-borne. Manifestly, pathological conditions of the seminal vesicles are of necessity restricted to the male. Pattern baldness, an autosomal gene, yields a character that is likewise restricted to the male, but for the reason that it is a gene that can find expression only in a male somatic milieu.

But crossing over between the homologous portions of the X and Y means that Y-borne gene material can be incorporated in the X and *vice versa*. These segments behave as do autosomes in this respect, and therefore the mode of inheritance of dominant and recessive characters with genes resident in these pairing segments of the X and Y will be similar to that of autosomal characters, but with this difference: variations in the frequency of crossing-over will result in a sex-ratio among the affected offspring that is significantly different from that of equality which obtains in

the case of autosomal characters. Though this is a matter that is intellectually attractive it is one that has no practical value in clinical genetics.

Examples total colourblindness, xeroderma pigmentosum, Oguchi's disease, recessive epidermolysis bullosa, dominant and recessive forms of retinitis pigmentosa.

Such evidence as presently exists seems to indicate that the dominant and the recessive genes which yield retinitis pigmentosa are, in fact, alleles—that is to say, each occupies the same locus in the X, each being a mutant form of the "normal" gene.

Multiple Allelomorphic Series

Mutation implies an alteration in the internal organization of a gene resulting in a changed action of that gene and yielding a different end-result. The gene undergoes change, but the developmental processes it affects remain the same. The mutant gene occupies the same locus in the chromosome as did the unmutated gene from which it arose and which it replaces. In this locus there can be one or the other but not both. The original gene or its mutant form can mutate again and again to yield a series of multiple allelomorphs, of which only one can occupy the particular locus. Since there are two chromosomes in every pair (the non-homologous section of the Y being disregarded), it follows that an individual can possess any two members of a multiple allelomorphic series.

Such a series, of the greatest interest to the clinician, is the A_1, A_2, A_3, B and O of the blood-group characters, A_1 being dominant to A_2, A_3 and O , A_2 to A_3 and O , A_3 to O , and B to O . When any of the A's and the B are present in the same individual, both are expressed.

Conclusion

This brief and most imperfect review may have sufficed to display the gifts that genetics offers to clinical medicine and to disclose the difficulties that surround them. It is manifest that rarely can the clinician expect to receive simple, straightforward, unequivocal answers to the questions he asks. Well may he doubt the usefulness to himself of a science whose every utterance seems to demand elaborate qualification. It cannot be that the complexities of the science repel him. He readily turns for help to biochemistry, a science no less specialized or complicated. But biochemistry places tools in his hands that he can profitably use in diagnosis and therapy. It does not deal so much with causes as with the nature and production of causes. Diabetes mellitus is in certain instances the expression of a dominant autosomal gene whose action is to yield abnormality in the functioning of the pancreas. Neither geneticist nor clinician can reach the gene, but the biochemist can demonstrate the nature of the effects of the action, discover insulin, and place an instrument of great potency in the hands of the clinician. Insulin therapy owes nothing to the gene. The geneticist can help to prevent the occurrence of diabetes mellitus in the next generation, the biochemist can provide the means of control of this condition in the existing generation. The treatment of haemophilia is not influenced by the fact that its causal gene is an X-borne recessive, though the explanation of its aetiology and incidence is solely genetical.

The main role of genetics in clinical medicine has been that it has furnished scientific factual knowledge on which advice concerning habits, behaviour and reproduction can

be built. Since the patients of the clinician are the children yet unconceived no less than the individuals of the existing generation, genetics can rightly claim a place in his equipment.

It has been the expansion of blood transfusion as a service that has given to genetics a firm and prominent place in clinical medicine. The knowledge which is purely genetical and which relates to the blood-group characters is now an essential part of the equipment of the modern clinician. The A B O multiple allelomorphous series, the M and N genes, the Rhesus genes, are as familiar to the clinician, the obstetrician, the pediatrician, as are any of the causal agents of bacteriology. In order to deal with their effects it is necessary to know them, and to know them is to know

genetics and to appreciate the value of this science in its applications to clinical medicine.

If medicine and the rest of the sciences that are being used by society for its own betterment flourish there will come a time when the environmental agencies that evoke disease are conquered. Then will be disclosed the hard core of the genetical varieties of physical frailty and mental defect and deficiency, for the treatment of which genetical measures derived from genetical knowledge may be required. For this reason it is desirable that even now every effort should be made to expand our knowledge of human genetics in order that, when wanted, the appropriate instruments of therapy may be found sharpened and ready in our armamentarium.

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VITAL STATISTICS OF STILL-BIRTHS AND NEONATAL DEATHS

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A still-birth is a baby of 28 weeks or more maturity since conception, who is delivered without showing any signs of life. Just before the war, there were about 25,000 still-births registered in England and Wales every year. About 607,000 babies were born alive, and of these, about 18,000 were dead within four weeks and 35,000 within a year. The total wastage of life during birth and infancy was thus about 60,000 a year. The natural increase (excess of live births over deaths at all ages) was about 119,000 a year. An annual loss of 60,000 potential citizens, in a period of public concern about the imminent decline in the country's population, is obviously a matter calling for serious investigation. I propose in this paper to state and discuss some of the facts about the vital statistics of still-births and deaths in early infancy, with special attention to the light they throw on the question of how far these deaths can be regarded as avoidable at the present stage of medical and social knowledge.

About half the infant deaths before the war were certified as due to infectious processes, the big cause-groups being bronchitis and pneumonia, diarrhoea and enteritis, and the common infectious diseases, mainly whooping cough and measles. The great majority of these deaths occurred in infants more than a month old. The other half of the infant deaths was ascribed to the group of causes sometimes called "developmental and wasting diseases", and sometimes "congenital causes", and mainly affected infants during the first four weeks of life. There are thus good grounds for making a distinction between neonatal deaths (at ages less than four weeks) and postnatal deaths (these during the remainder of the year of infancy). Still-births and neonatal

deaths form a natural aetiological grouping, in which the main influences are foetal defects, unfavourable intra uterine conditions, the hazards of the birth process, and adverse environmental circumstances acting on the child indirectly through the mother.

During the five years 1934 to 1938 inclusive, the average infant mortality in England and Wales was 56.9 deaths per 1,000 live births, of which the neonatal rate was 30.0. Deaths in the "congenital causes" group gave a rate of 30.9. The rates attributed to the various diagnostic categories included under this heading are shown in Table I. More than half the deaths are associated with prematurity, and one fifth with congenital malformations.

TABLE I. DEATHS FROM "CONGENITAL CAUSES" MORTALITY-RATES PER 1,000 LIVE BIRTHS, ENGLAND AND WALES, 1934-38

Congenital malformations	6.02
Congenital debility	2.30
Premature birth	16.83
Atelectasis	1.95
Icterus neonatorum	0.53
Disease of the umbilicus	0.13
Pemphigus neonatorum	0.11
Other diseases of early infancy	0.53
Injury at birth	2.46
Total	30.86

These national averages conceal quite wide differences between different strata of the population. An indication of the variation in the rates with social and economic status is provided by Table II. In his 1931 *Decennial Supplement*,

TABLE II. MORTALITY FROM CONGENITAL CAUSES FOR LEGITIMATE INFANTS BY SOCIAL CLASS OF FATHER, ENGLAND AND WALES, 1930-32

Social class	I	II	III	IV	V	All
Congenital malformations	5.0	5.4	5.6	5.7	5.4	5.5
Congenital debility	1.4	2.2	2.9	3.3	3.8	3.0
Premature birth	10.5	14.4	16.8	18.6	19.6	17.3
Injury at birth	2.3	2.5	2.1	2.0	2.0	2.1
Other causes	2.8	3.0	2.7	2.9	3.0	3.0
Total	22.0	27.5	30.1	32.5	33.8	30.9

part IIa (occupational mortality), the Registrar-General divided the occupied males into five social classes. Class I comprised the higher business and professional occupations, Class III the skilled workers, and Class V the unskilled. The other classes were intermediate, Class II being mainly the lower professional and business grades, and Class IV semi-skilled workers. The average infant mortality during 1930-32 is given for each class, analyzed by cause and by age at death. The table shows the rates for the congenital causes group, and for the various sub-headings in so far as they are separately distinguished. It will be seen that the total mortality of 33.8 in Class V is more than 50% higher than the rate in Class I. Congenital malformations and other causes show no consistent class gradient, and injury at birth decreases slightly as one descends the social scale. But congenital debility and premature birth go up quite steeply with increase in poverty. Class V shows nearly double the mortality of Class I from premature birth, and over 2½ times the rate for congenital debility. The whole of the difference between Class I and Class V is accounted for by the excess under these two headings.

Still-birth rates are usually calculated by the formula

$$\frac{\text{Number of still-births during year}}{\text{Number of live births + still births during year}} \times 1000$$

The rates are thus not quite comparable with those for infant mortality, which are given per 1,000 live births. In England and Wales during 1934-38, the still-birth rate, calculated as above, was 39.7. The still-birth rate, per 1,000 live births, was 41.3, as compared with the neonatal mortality-rate of 30.0. In England and Wales there are no figures available for still-births analyzed by cause or by social class.

Registration of still-births in Scotland did not begin until 1939, and an analysis for this year by social class of father was made by the Registrar-General for Scotland. The results are shown in Table III. It will be seen that in the

TABLE III STILL-BIRTHS ACCORDING TO SOCIAL CLASS OF FATHER, SCOTLAND, 1939. RATES PER 1,000 TOTAL BIRTHS, LIVE AND STILL

	Social class					
	I	II	III	IV	V	All
Large burghs	30.0	35.5	41.8	43.1	44.0	42.1
Countries (excluding large burghs)	38.7	39.6	48.7	33.6	39.0	42.5
Scotland	33.9	37.8	44.5	38.0	42.4	42.2

large burghs (the 24 largest towns) the rate rises steadily with fall in economic status, Class V having a rate about 50% higher than that for Class I. In the county areas there is no clear trend, and Class III gives much the highest rate. This anomalous result may be at least partially explained by the mode of allocation of occupational groups to the different social classes. In particular, mortality-rates among infants of coal miners are excessively high. This is discussed below. The majority of coal miners are assigned to Class III, and there are probably enough miners in the Scottish counties to give an anomalously high figure for Class III. Nevertheless, the irregularity of the figures for Scottish counties does suggest that economic status is not the only important social agency influencing the incidence of still-births.

In Scotland, but not in England and Wales, the law requires registration of the cause of each still-birth. The data are tabulated in considerable detail by the Registrar-General for Scotland, and the figures for 1939 to 1943 are summarized in Table IV. In view of the difficulty of fixing the cause of a

TABLE IV CAUSES OF STILL BIRTHS, SCOTLAND, 1939-43. RATES PER 1,000 TOTAL BIRTHS, LIVE AND STILL

	1939	1940	1941	1942	1943	Mean
General diseases in mother	0.9	0.9	1.3	1.2	1.2	1.1
Toxaemias in mother	3.8	4.4	4.0	4.2	3.4	4.0
Ante partum haemorrhage	5.4	5.0	5.1	5.2	4.3	5.0
Difficult labour	9.5	8.9	11.3	10.4	9.3	9.9
Foetal malformations	5.9	6.1	6.5	6.8	6.1	6.3
Other defined causes	2.9	3.1	3.2	4.2	4.5	13.3
Undefined causes	13.9	13.7	8.1	6.3	6.9	
All causes	42.2	42.1	39.6	38.2	35.6	39.6

still-birth with any certainty, the table shows remarkably high consistency in the main cause groups from year to year. The only large change has been a fall in the undefined causes and a corresponding rise in the miscellaneous defined causes. It may be taken that certification, if not accurate, is at any rate biased in the same way in different years. The mean rates for the five years can be summarized as follows:

Conditions affecting the mother (general diseases toxaemias and haemorrhage)	10.1
Difficult labour	9.9
Foetal malformations	6.3
Other causes defined and undefined	13.3
Total	39.6

To obtain the total mortality from congenital malformations, one must combine the still-birth rate and that for live-born infants. In Scotland, during 1939-43, the average infant mortality from congenital malformations, calculated per 1,000 total births, was 6.3—exactly the same as the rate among still-births. The total mortality was thus 12.6 per 1,000 total births, or 13.0 when reckoned per 1,000 live births.

Still-birth and neonatal mortality-rates are influenced by three groups of etiological agencies:

- 1 Biological
- 2 Social and economic
- 3 Medical and nursing facilities

The biological differentials include parity of birth, age of mother, and sex of infant.

Birth-Parity and Maternal Age

Figures showing the variation in still-birth rates with parity and age of mother are shown in Table V. The data are

TABLE V SINGLE STILL BIRTHS PER 1,000 SINGLE LIVE-BIRTHS BY PARITY AND AGE OF MOTHER, ENGLAND AND WALES, 1939-40

Age of mother	Order of birth														All
	1	2	3	4	5	6	7	8	9	10	11	14	14	14	
15-19	27	18	—	—	—	—	—	—	—	—	—	—	—	—	26
20-24	29	18	23	31	—	—	—	—	—	—	—	—	—	—	26
25-29	39	21	24	29	33	34	—	—	—	—	—	—	—	—	31
30-34	57	27	31	35	38	39	42	42	—	—	—	—	—	—	39
35-39	82	39	40	48	50	51	55	62	63	68	68	68	68	68	52
40-44	113	59	57	59	77	71	72	67	72	71	80	80	80	80	71
45-49	—	—	—	—	—	—	—	—	—	—	—	—	—	—	101
All	40	25	30	38	45	48	52	57	66	70	77	77	77	77	36

for England and Wales in 1939-40, and refer only to single births, it being impossible, from the Registrar-General's tabulations, to include twin and triplet maternities. But the difference that this omission makes to the general picture is negligible. All rates shown are based on at least 80 deaths

The table shows the following features:

At any given birth-parity, the still-birth rate increases steadily with age of mothers.

At any given maternal age, the rate is highest for the first-born, lowest for the second-born, and then increases slowly with increase in parity.

There are no national figures relating neonatal death-rates to age of mother or birth-parity. But various special studies, including those of Burns (1942) in the County of Durham, of Baird (1945) in Aberdeen, and of Woodbury (1925) in a number of towns in the USA, agree in the conclusion that, at any given maternal age, the pattern of neonatal mortality-rates in relation to birth rank is similar to that for still-births. They also find that mortality-rates are higher for the older mothers, but there is a suggestion that rates may be rather higher for mothers below twenty years of age than for those in the early twenties. It is desirable that the question should be investigated on a large enough scale to give reliable rates in all sub-groups.

Sex Ratio

Male still-births number about 120 for every 100 female still-births. Neonatal mortality-rates among male babies are about 125% of the female rate. But when the total rates are analyzed by cause, curious differences appear. Table VI

TABLE VI RATIO OF MALE TO FEMALE STILL-BIRTHS, SCOTLAND, 1939-43

	1939	1940	1941	1942	1943	Mean
General diseases in mother	1.08	1.77	1.72	1.13	1.42	1.42
Toxaemias in mother	1.18	1.39	1.58	1.36	1.21	1.34
Ante-partum haemorrhage	1.41	1.24	1.36	1.26	1.36	1.33
Difficult labour	1.68	1.72	1.56	1.61	1.35	1.58
Foetal malformations	0.64	0.69	0.63	0.57	0.60	0.63
Other defined causes	1.19	1.28	1.49	1.23	1.20	1.28
Undefined causes	1.27	1.28	1.28	1.37	1.11	1.26
All causes	1.28	1.26	1.27	1.19	1.11	1.22

gives the ratio of male to female still-births in Scotland in the main cause groups. There is a substantial male excess in all cause groups except foetal malformations, where the female still-births outnumber the male by more than 3 to 2. Male foetuses are more liable than female to succumb to the perils of the process of being born, but the incidence of lethal defects in the foetus itself is higher among females. The relative sex incidence varies greatly for different kinds of malformations, as is shown in Table VII. The largest single

TABLE VII STILL-BIRTHS FROM FOETAL MALFORMATIONS, SCOTLAND, 1939-43

	Total	Male	Female	Ratio male to female
Anencephalus	1,180	325	855	0.38
Hydrocephalus	604	318	286	1.11
Multiple malformations	351	132	219	0.60
Spina bifida	236	95	141	0.67
Others	544	249	295	0.84
Total	2,915	1,119	1,796	0.62

category of malformations, anencephalus, was responsible for 1,180 still-births in the five years in Scotland. The male to female ratio was 0.38. Hydrocephalus showed a slight male excess, but all other kinds of malformation, with two very minor exceptions, predominated in female foetuses.

There is a similar wide variation in the sex incidence of deaths among live-born infants from congenital malformations. This is shown in Table VIII, which is condensed from

TABLE VIII RATIO OF MALE TO FEMALE DEATHS AMONG LIVE-BORN INFANTS FROM CONGENITAL MALFORMATIONS, ENGLAND AND WALES, 1931-35

Pyloric stenosis	3.88
Imperforate anus	3.07
Cleft palate, hare lip	1.66
Other malformations of digestive tract	1.49
Heart	1.41
Hydrocephalus	1.27
Other malformations of central nervous system	0.83
Other skeletal malformations	0.74
Spina bifida, meningocele	0.70
Monstrosities	0.67
Naevi	0.53

a table given in the annual report of the Registrar-General of England and Wales (text, 1936).

The ratio of male to female deaths varies from 3.88 to 0.53, and in no category is it even approximately unity. It is interesting to note that in the two categories that appear in Tables VII and VIII—hydrocephalus and spina bifida—the sex ratio among still-births is very similar to that among live-births.

Extent of Influence of Social Factors not Apparent from Crude Statistics

Some of the evidence for attributing great influence to social and economic conditions has already been given in Tables II and III. Still-birth rates, and infant mortality from prematurity and the unsatisfactory diagnosis of "congenital debility", increase steadily from Class I to Class V. The Registrar-General's analysis by social class does not display the full extent of difference in the rates in different sections of the population. The worst county boroughs in England and Wales, for example, show considerably higher still-birth and neonatal death-rates than those for Class V as a whole. Nor do observed differences in rates between social classes express the full effect of economic conditions, because of the class gradient in fertility. The average number of children per family in Class I is less than in Class V. There will therefore be a larger number of first-born per 1,000 births at the higher social level, entailing a bigger mortality risk. Increasing poverty and increasing size of family pull in opposite directions in their effects on still-birth and neonatal death-rates. If one could subdivide the births in Class I and Class V by parity and age of mother, and compare the rates in each sub-group, the contrast would necessarily be greater than that found between the crude figures, which take no account of the differences in biological composition of the social classes with respect to birth parity and age of mother.

Influence of Maternal Nutrition and of Medical Care

There is a consensus of medical opinion, expressed in such articles as that of Young (1945), that still-birth and neonatal rates are greatly influenced by maternal nutrition in the prenatal period. The evidence, which there is no space to consider fully here, is reviewed in a paper shortly to be published by Woolf (1946), and is discussed also by Huggett (1946) in this number. Woolf also subjects the still-birth and neonatal mortality-rates in county boroughs of England and Wales to a process of multiple regression analysis similar to that employed in a published study by Woolf & Waterhouse (1945). He finds that both rates tend to increase with decreasing size of family. When this is allowed for, still-birth rates are very sensitive to increases in the percentage of men unemployed or in low-paid occupations, but are hardly

affected at all by indices of overcrowding. This is consistent with the view that poverty exerts its influence primarily through malnutrition. Among neonatal deaths, the indications are that overcrowding and malnutrition are both of importance. This aetiological differential is supported by changes in the rates during the war. There has been an improvement in nutrition among the poorest section of mothers, due to the abolition of unemployment, the upward levelling of earnings, and the nutritional policy of the Government. On the other hand, housing conditions probably deteriorated. Between 1938 and 1944, still-birth rates dropped from 39.8 to 28.5, a fall of 11.3, but neonatal mortality dropped only by 3.8, from 28.3 to 24.5.

Woolf also gives an account of the evidence that still-birth and neonatal rates can be drastically reduced by improvements in the standards of medical and nursing care. Besides special studies like that of Baird (1945), this proposition is supported by much indirect statistical evidence. It is only by this means that one can account for the very low rates in Greater London, and the abnormally high rates among mining communities, which are still evident when differences in crowding, poverty and size of family are fully taken into account.

In summing up, it is convenient to consider congenital malformations separately from the other categories of still-births and neonatal deaths. The majority of still-births seem to arise from the hazards of the birth process. This must depend greatly on intra-uterine conditions, since the risk varies so much with birth parity and maternal age. There are good grounds for believing that the intra-uterine environment is also adversely affected by maternal malnutrition, and that the hazards of birth can be substantially diminished by antenatal and obstetric care. Neonatal deaths, whether ascribed to prematurity or not, are much more frequent in premature than in full-term infants. The incidence of prematurity can be reduced by improved social conditions, especially nutritional, and by better professional care, which can also prevent many deaths when prematurity has occurred (cf. Crosse, 1945). Death-rates in all these categories could also be reduced by an increase in the average size of family and a decrease in the average maternal age.

Congenital Malformations

Congenital malformations seem to differ from the other categories of still-births and neonatal deaths. Here there seems no basis for sober optimism, nor any indication of a plan for attacking the problem. It seems that such defects arise during the process of fertilization of ovum by spermatozoon, and that nothing we may do afterwards can undo the damage. That may turn out to be the case. But there are some things about congenital malformations that need

investigation before this pessimistic conclusion can be accepted. Firstly, there are the curious differences in sex-ratio in the various kinds of malformation. These form a

TABLE IX STILL BIRTHS FROM FOETAL MALFORMATIONS PER 1,000 TOTAL BIRTHS BY MATERNAL AGE, SCOTLAND, 1939-43

Age of mother	1939	1940	1941	1942	1943	Mean
Under 20	4.0	5.5	5.5	5.6	2.9	4.7
20-24	4.1	4.5	5.2	5.6	5.1	4.9
25-29	5.4	5.5	5.5	5.7	4.7	5.4
30-34	6.7	6.2	7.2	7.3	7.0	6.9
35-39	7.8	9.1	9.7	9.2	8.6	8.9
40 and over	9.5	10.8	9.4	11.2	9.5	10.1

challenge to medical geneticists, and their investigation might well bring to light new facts about human malformations that would provide the basis for preventive action. Secondly, there is some evidence that the death-rate from congenital malformations depends on intra-uterine environment and is not solely determined by gene interactions at fertilization. Apart from the case implicating maternal rubella, discussed elsewhere (Parsons, 1946) in this number, there are the following indications:

1 Deaths from congenital malformations are abnormally high in occupational groups where women do prolonged or heavy work during pregnancy.

2 Deaths from congenital malformations, like other categories of neonatal mortality, are abnormally low in Greater London. Can this be an effect of better antenatal and obstetrical care?

3 The still-birth rate from congenital malformations varies greatly with age of mother. The figures for Scotland are shown in Table IX. It is difficult to explain the rise in rate with maternal age except as indicating that intra-uterine conditions must have a marked influence on the genesis of foetal deformities.

It is, of course, true that the figures show only death-rates, and not incidence-rates of foetal malformations. It may be that large numbers of foetal monstrosities are aborted early in pregnancy, and that there is a sex difference in abortion rates. It may be that in some cases—e.g. cleft palate—a substantial proportion of affected individuals are viable, and that the sex-ratio among these is different from that among those who succumb. Taking still-births and live-births together, the total loss of infant life from congenital malformations is greater than the combined figure for measles, whooping-cough and diarrhoea and enteritis. The problems briefly touched on here are surely worth a full-scale investigation.

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THE PATHOLOGY OF STILL-BIRTH AND NEONATAL DEATH

A review of 1053 cases

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Recent years have seen an awakening of interest in the problem of neonatal mortality. Pathological studies of the causes of foetal and neonatal death have helped materially to define the extent and nature of the problem, and have revealed certain facts of the greatest importance, which formerly were not appreciated. It has been shown that clinical diagnosis, when unconfirmed by post-mortem findings, is liable to be inaccurate. This is not surprising, as the clinical manifestations, even of grave disease in the newly born, can be extremely obscure and misleading even to the most skilled observers. This is therefore one of the branches of medicine in which the close co-operation of a pathologist can be of the utmost value to clinical workers, and it is regrettable that even now, despite much improvement in recent years, the pathology of still-birth and of the neonatal period is still a somewhat neglected field.

The following brief review of the subject is based on the experience of the writer as pathologist to a large maternity hospital, where it has been the practice for many years to perform necropsies on all live-born babies that die in hospital, except for the very few for which permission is refused by the parents, and also on a large number of dead-born foetuses. The results presented may therefore be accepted as fully representative of the foetal and neonatal mortality of the hospital.

TABLE I CAUSES OF FOETAL DEATH IN 435 CASES OF STILL-BIRTH

Condition	Full time	Premature	Total	Per cent
Developmental defects	23	65	88	20.2
Intracranial haemorrhage	68	37	105	24.1
Asphyxia	94	68	162	37.2
Infections	11	3	14	3.2
Miscellaneous	10	11	21	4.8
Not ascertained	12	51	63	10.3

TABLE II CAUSES OF 618 NEONATAL DEATHS

Condition	Full time	Premature	Total	Per cent
Developmental defects	42	23	65	10.5
Intracranial haemorrhage	31	140	171	27.6
Asphyxia	14	67	81	13.1
Infections	64	126	190	30.7
Miscellaneous	24	25	49	7.9
Prematurity only	—	55	55	9
Not ascertained	7	—	7	1

Table I presents the pathological findings in 435 cases of still-birth, and Table II those in 618 cases of neonatal death, arranged according to what was deemed to be the principal cause of death. From these it is evident that the majority of cases of still-birth fall into one of three main categories—defects of development, asphyxia, and intracranial haemorrhage—while in cases of neonatal death a fourth important group is added—infective diseases. These four categories included over 80% of both still-births and neonatal deaths, and are therefore of such great importance that they must be dealt with in some detail.

Defects of Development

Developmental defects were found in 20% of the still-births and 10.5% of the neonatal deaths. There is a great variety of these conditions that may prove incompatible with the establishment or continuance of independent existence after birth. They are not preventable, and their interest is embryological rather than pathological or clinical. No detailed description of these conditions or discussion of the embryological problems concerning them is appropriate here, but brief mention may be made of some of the commoner forms of maldevelopment.

Congenital cardiac defects are more often a cause of neonatal death than of still-birth. They occur in endless variety. Those that cause death in the neonatal period are often complex and of severe grade. Anencephaly is relatively common as a cause of still-birth. Very occasionally an anencephalic foetus is born alive, but they never survive long. Spina bifida is one of the commonest developmental malformations, most often affecting the lumbosacral region, and usually associated with meningocele or meningo-myelocele, and often with congenital hydrocephalus. These infants are most often full-term and born alive. Sometimes in cases of occipital meningo-encephalocele, the whole brain lies outside the cranium, within the sac, and the low, flat vault of the skull, enclosing a tiny cranial cavity, gives an appearance resembling anencephaly. Such infants, occasionally survive for several days.

Diaphragmatic defects, with displacement of abdominal organs into the thorax, are less rare than is often thought. They are much commoner on the left side than on the right. The most usual type is the so-called "false hernia," where the pleural and peritoneal sacs are in continuity through the defect in the diaphragm, and the displaced viscera are not enclosed in a hernial sac. Sometimes, however, the two serous cavities are not continuous, and the displaced abdominal viscera have a covering composed of peritoneal and pleural membrane, which separates them from the thoracic organs. In cases of diaphragmatic hernia it is usual to find that the lung on the affected side is imperfectly developed, sometimes vestigial.

Developmental defects of the urinary system are among those most often encountered. Absence of both kidneys is an occasional cause of early neonatal death. Extreme cases of bilateral renal hypoplasia and of polycystic disease may be incompatible with life beyond a few days or weeks. Congenital hydronephrosis does not often cause death so early, but may be found when death is due to another cause. The writer has been impressed with the frequency with which developmental errors of the genito-urinary system accompany other defects, which may be of a more lethal nature. Thus the pathologist whose work is with newly born infants and

foetuses comes to regard such conditions as absence or extreme hypoplasia of one kidney, horse-shoe kidney, and double ureter or pelvis, as fairly common occurrences, while he whose work is with older subjects regards them as rarities

Asphyxia

Asphyxia resulting from stress of birth or accidents such as antepartum haemorrhage or prolapse of the cord is among the most important causes of still birth and neonatal death. It accounted for 37.2% of the still births and 13.1% of the neonatal deaths in the writer's series. The degree of asphyxia suffered by the foetus may be sufficient to cause death before delivery. Such foetuses will show at autopsy clear signs of asphyxia: multiple subserous petechial haemorrhages, especially in the thorax, haemorrhages in the thymus and lungs, dilatation of the right side of the heart, extreme venous engorgement throughout the body, and dark, fluid blood. In addition, the asphyxiated foetus may have passed meconium into the liquor amni and inhaled it. The colon will then be found empty, and the respiratory passages full of greenish fluid, the lungs being sometimes so full that they are to some extent expanded, and are bulky and heavy like pneumonic lungs, and of a green tint.

More commonly, without passage of meconium, asphyxia may stimulate the foetal respiratory centre so that attempts at respiration are made before the child is born, with the result that the lungs are flooded with liquor amni. This can be recognized under the microscope by the presence of solid debris, which is suspended in the liquor amni. Cornified cells, lanugo hairs, and masses of vernix caseosa, all derived from the skin of the foetus, are found in large quantity in the lungs.

Although there is some difference of opinion as to whether any liquor amni normally enters the foetal lungs, there is little doubt that any considerable quantity is abnormal and indicates severe foetal asphyxia. This is a common finding both in still-births and in asphyxiated infants that are born alive. In the latter, the water-logged state of the lungs interferes seriously with the establishment of respiration, and the presence of so much solid material may, of itself, prevent proper aeration. Especially is this the case when the foetus has inhaled masses of vernix. This material, when found in unaerated lungs, is in solid lumps, but, when air enters, the vernix becomes plastered against the walls of the air-spaces as a membrane, which may form a complete lining in bronchioles, alveolar ducts and alveoli. This causes most serious obstruction to the passage of air, and is usually accompanied by extreme atelectasis, while areas of lung into which air does enter may become over-inflated, producing acute emphysema, which is often of interstitial type: air bullae form in the interlobular septa and pleura, and the rupture of subpleural bullae is an occasional cause of spontaneous pneumothorax in the newly born.

Asphyxiated infants suffer, not only from mechanical effects of inhaled liquor amni, but from depressed activity of the respiratory centre, which is the direct result of asphyxia when it reaches the degree at which stimulation is succeeded by depression or paralysis. Such infants do not cry well and may continue for some hours, or even a day or two, with shallow breathing which never adequately expands the lungs. If an infant remains in this condition until death, the lungs are found in a state of almost complete atelectasis.

They may be macroscopically indistinguishable from the lungs of a foetus that has never breathed, and they sink heavily in water. Microscopical examination reveals that air has penetrated only to some of the bronchioles and alveolar ducts, and there may be no aeration of alveoli. This condition may be found in an infant that has lived as long as 24 hours. If an infant continues thus into the second or third day, the lungs almost inevitably develop an increasing oedema, and, as will be seen later, are very prone to become the seat of pneumonia.

The extreme venous engorgement that accompanies asphyxia may be a cause of severe and fatal haemorrhage at various sites, to which reference will be made later.

Intracranial Haemorrhage

Intracranial haemorrhage was responsible for 24.1% of the still-births and 27.6% of the neonatal deaths in the writer's series of cases. Three distinct types are common: subdural, subarachnoid, and intraventricular.

Subdural haemorrhage is perhaps the most familiar. It results directly from birth trauma that causes tearing of intracranial veins. The commonest site of injury is the tentorium cerebelli. Especially when the free margin is damaged, a vein is liable to be torn across and free haemorrhage into the subdural space results. Less often, the falx cerebri is the site of the tear, which may cause severe haemorrhage if the inferior sagittal sinus is involved. An occasional cause of very severe haemorrhage is rupture of the great cerebral vein, usually close to its point of entry into the straight sinus (sinus rectus). Subdural haemorrhage is apt to occur under circumstances that cause excessive moulding or compression of the foetal head: disproportion, obstructed labour from various causes, and instrumental deliveries. It is to be expected that a majority of cases should be in full-term babies, and this is the case, but it is noteworthy that the number of cases in premature infants is large in proportion to the number of premature births.

Subarachnoid haemorrhage is less important, though it is a frequent finding in both still-births and neonatal deaths. Except when it is secondary to intraventricular haemorrhage, the bleeding comes from veins in the leptomeninges over the surface of the brain. It is considerably commoner in premature than in full-term infants, and, as evidence of severe asphyxia is usually present, and there is often a history of some condition such as antepartum haemorrhage, which would be likely to cause foetal asphyxia, the haemorrhage can usually be explained as a result of asphyxial venous engorgement. Under these conditions, haemorrhage is probably more likely to result in the premature, owing to the immaturity of the veins, in which the muscle and elastic tissue are not fully developed. Subarachnoid haemorrhage is not often very severe, and is probably seldom in itself a direct cause of death. Blood effused in this situation is readily absorbed, and there is little risk that it will become organized. There is therefore no reason to suppose that it often produces permanent harmful effects, though the writer has seen hydrocephalus result from organization of a subarachnoid haemorrhage at the base of the brain.

Intraventricular haemorrhage is much more deadly. It is of interest in that it is almost entirely a disease of the premature. In a consecutive series of 156 cases of intraventricular haemorrhage examined by the writer, only 7 were

in full-term babies. It is not very often found in still-births (only 19 of the 156 cases were still-births), it is most frequent in live-born infants that die on the first day, and although it may be encountered late in the neonatal period, it is rather uncommon after the first week. The source of the haemorrhage is usually a vein in the floor of one of the lateral ventricles, most often the terminal vein, which runs in the groove between the thalamus and the caudate nucleus. Haemorrhage occurs first under the ependyma. If this ruptures, free bleeding takes place into the ventricles. Sometimes the source of the haemorrhage is the choroid plexus. In a severe case, the whole ventricular cavity may be filled with blood-clot, which forms a complete cast of all the entricles and aqueduct. As some blood usually escapes into the subarachnoid space, intraventricular haemorrhage is usually accompanied by subarachnoid haemorrhage. It may cause a great increase of intracranial pressure, and it is probably rapidly fatal in most cases. At necropsy, there is usually evidence of asphyxia at birth, but there may be other aetiological factors not as yet understood. It is probable that the haemorrhage into the ventricles does not usually occur until a variable time after birth, but it may be that the subependymal haemorrhage takes place as a result of birth-asphyxia, the rupture through the ependyma being delayed for some hours or days.

A less common type of haemorrhage, sometimes associated with intraventricular haemorrhage, is when bleeding occurs into the brain-substance in the central part of the cerebrum. Sometimes this is associated with thrombosis of the choroidal and great cerebral veins.

Another infrequently-encountered type of intracranial haemorrhage is extra-dural, which is the result of severe trauma, with rupture of sutures or fracture of the parietal bone, when the most probable source is injury to the middle meningeal artery.

Infective Diseases

Perhaps the most valuable contribution that pathology has made to knowledge of disease in the newly born is the revelation of the immense importance of infection as a cause of neonatal death.

TABLE III. CAUSES OF 241 NEONATAL DEATHS AFTER THE THIRD DAY

Condition	Number	Per cent
Developmental defects	20	8.3
Intracranial haemorrhage	22	9.1
Asphyxia	1	0.4
Infections	158	65.5
Miscellaneous	40	16.6

Infection was responsible for 3.2% of the foetal deaths and 30.7% of the neonatal deaths in the writer's series. Table III, which deals with the same series of cases as Table II, but excludes all deaths in the first 3 days, reveals that among those babies that survived the immediate risks of birth, and died during the first month, almost two-thirds died of infective diseases. This is a fact that would have been thought incredible a few years ago, when less was known about these matters, and even yet it is not appreciated as it should be. The importance of this fact cannot be exaggerated, for it is in this group that most improvement in mortality may be anticipated as a result of preventive measures.

Respiratory Infections

The common lethal infections are those of the respiratory tract, especially pneumonia, and those of the alimentary tract, including neonatal gastro-enteritis and severe thrush affecting the oesophagus and sometimes the stomach and intestine. Of these, much the most common is pneumonia. This has some forms that are peculiar to the neonatal period, and some that are commoner then than at other ages.

In the first week, and especially in the first three days, pneumonia usually affects lungs in which an abnormal condition has developed as a result of birth stress. As has already been said, lungs that are atelectatic, oedematous, or filled with liquor amnii as a result of birth-asphyxia, are very prone to develop pneumonia, infection being contracted either during birth from the maternal passages, or after birth from the environment. In pneumonia of this type, consolidation is seldom massive and its presence is masked by atelectasis and oedema. It is therefore easily missed at necropsy, though the experienced pathologist will usually detect an altered consistence by which its presence may be suspected even when it is not visible to the eye. Microscopical examination reveals pneumonia in many cases in which it is not detected at necropsy.

In the later weeks of the neonatal period, pneumonia is seen in forms that occur also in older infants. Typical bronchopneumonia tends to be massively confluent. As in older infants, it may be caused by the common pathogens of the respiratory tract—*Strep. haemolyticus*, *Pneumococcus*, *H. influenzae*—but cases that are typical pathologically may be due to infection with organisms that do not have such effects in older subjects, notably those of the *B. coli* group. This is an interesting feature of other neonatal infections besides pneumonia.

Two other types of pneumonia must be mentioned because, though not confined to the neonatal period, they are commoner then than at a later age. Septic aspiration pneumonia, due to inhalation of milk or, more often, of regurgitated or vomited gastric contents, produces widespread consolidation with haemorrhage and a purulent type of exudate, among which are found masses of aspirated foreign material and bacteria, and the action of the gastric juice, causing lysis of blood and digestion of tissue, gives the microscopical picture easily recognized characters. It should be emphasized that this is a common type of neonatal pneumonia. The other special type is staphylococcal pneumonia. This is essentially a disease of infancy, and it is relatively common in the newborn. It may be caused by inhalation of milk containing *Staph. aureus*, but not all cases can be so explained; some result from infection transferred from the baby's environment, from the attendants or other babies in the nursery. Cases occur sometimes in association with outbreaks of other types of staphylococcal infection in hospital nurseries. The condition affects one or more large areas of the lung. Suppuration develops rapidly in the bronchi and spreads to the alveolar tissue, multiple abscesses form, and the part undergoes complete disorganisation. Empyema and pyo-pneumothorax follow the rupture of abscesses into the pleural cavity. Death supervenes after an illness of a few days.

Alimentary-tract Infections

Neonatal gastro-enteritis is an epidemic disease that presents a grave problem in institutions. The bacterial cause

is unknown, despite much investigation. No known intestinal pathogen has been incriminated. Certain evidence points to a virus as the cause. Evidence that it may be secondary to a parenteral infection is less satisfactory than in the case of gastro-enteritis in older infants. The pathology is somewhat indefinite. Sometimes little is found apart from wasting and dehydration. But in many cases there is some evidence of an inflammatory condition, with severe congestion in the stomach and upper jejunum, sometimes with slight haemorrhage from the congested mucosa. Ulceration does not develop. In some cases the liver is enlarged and fatty, but this is not constant. In many cases a terminal pneumonia develops, often of the septic aspiration type, from inhalation of vomitus.

Thrush not uncommonly assumes a severe and dangerous form in the newly born, when the infection spreads from the mouth to the pharynx and oesophagus, less often to the stomach, and occasionally to the intestine. The thrush organism (*Monilia albicans*) forms masses, which adhere to the mucous surface as large flat plaques or small, sharply-defined raised nodules. The mucous surface under these is ulcerated to a varying depth, mycelium of the organisms may penetrate deeply into the wall of the organ. The amount of inflammatory infiltration varies, and is sometimes not great. Oesophageal thrush is a dangerous condition. The infants die of inanition or from septic aspiration pneumonia.

Other Infections

Other types of infection were relatively uncommon in the series of cases under consideration. Septicaemia and pyaemia from umbilical sepsis, skin infections, or other source, occasionally occurred. There were several cases of meningitis, due to the pyogenic cocci or to *B. coli*. This is another example of the unusual pathogenic effects of *B. coli* in the newborn. The writer has a record of only one fatal case of osteomyelitis, which ended in pyaemia. Renal infections are rarely fatal in the neonatal period. Congenital syphilis caused a small number of still-births but very few neonatal deaths. Its small part in the mortality is a tribute to efficient treatment of the mothers. It is the writer's experience that, if a syphilitic infant is born alive, it usually survives the neonatal period.

Miscellaneous Conditions

The most important of the various conditions that were included under this heading in the tables is haemolytic disease of the foetus and newborn (erythroblastosis foetalis). This disease has aroused much interest in recent years, since its cause was discovered in incompatibility of the blood of mother and foetus in respect of the Rhesus factor, which accounts for the vast majority of cases. Reference to this subject¹ must here be confined to brief mention of the various pathological types of the disease.

The least severe form, not often fatal, is anaemia haemolytica neonatorum, in which a severe haemolytic anaemia, without jaundice, develops soon after birth. The commonest form is icterus gravis neonatorum, in which jaundice develops at or soon after birth, becomes deep, and is associated with severe anaemia, and sometimes with cerebral symptoms referable to an associated "kernicterus", in which nerve-cells in certain nuclei of the brain undergo degeneration and become deeply bile-stained. Such cases are often fatal in

the early days of life, but some of the infants recover. More severe, invariably fatal, and usually a cause of still-birth rather than of neonatal death, is hydrops foetalis, in which a very severe general oedema is associated with profound anaemia, but usually no jaundice. These are the three well-recognized forms of the disease. But a fourth, and most severe, form occurs, which causes earlier intra-uterine death. The foetus is macerated when born and may not be hydropic.

All types have certain features in common: spleno- and hepato-megaly, with excessive extra-medullary haemopoiesis in the liver, spleen and elsewhere; excessive haemosiderin deposits in the liver and spleen; and a characteristic blood-picture, with abnormally numerous nucleated red cells, many of a primitive type, with corresponding changes in the bone-marrow. In the case of a macerated foetus, the characteristic blood-picture and other evidence of erythroblastosis may not be recognizable. In some of the more-severe cases, especially of hydrops, central-zone necrosis in the liver may be found, sometimes with an early replacement-fibrosis. In the type with maceration, this may have proceeded to a stage of diffuse fine fibrosis, which presents a picture so like that of congenital syphilis that many cases must undoubtedly have been ascribed to that disease, especially as there is usually a similar family history of repeated still-births. The principal distinguishing features between the two diseases are the presence of heavy haemosiderin deposits in the liver and the absence of spirochaetes in haemolytic disease, and the reverse in syphilis, and the results of serological tests for syphilis and of tests for the Rhesus factor and antibodies.

Other conditions that can only be mentioned among those included in the "Miscellaneous" group are haemorrhage in the suprarenal glands, in the peritoneal sac (usually from rupture of a subcapsular haematoma on the surface of the liver), in the lungs, and from acute ulcers in the duodenum or at the lower end of the oesophagus; obstructive lesions of the bowel other than those of developmental origin, most often volvulus of the small intestine, and rare cases of neoplasm.

Prematurity

One fact that emerges clearly from this study is the outstanding importance of prematurity as a factor in foetal, and more especially in neonatal, mortality. The figures given in Tables I and II show that 54% of the still-births and 70.5% of the neonatal deaths were in cases of premature birth. During the period covered by this series of cases, slightly over 10% of all live-births in the hospital were premature, and it was this 10% that produced almost three-quarters of the neonatal mortality. Except when it is extreme, prematurity is seldom the sole ascertainable cause of death, but its importance as a factor predisposing to death from almost every other cause cannot be exaggerated. In this series, among the live-born infants that died of asphyxia, 82.7% were premature, of those that died of intra-cranial haemorrhage, 81.8%, and of those that died of infection, 66.3%. This shows how close the problem of neonatal mortality is to that of prematurity, for nothing could make a greater contribution to a reduction in the neonatal death-rate than prevention of premature births.

Summary

Of 435 cases of still-birth and 618 of neonatal death, the majority of the cases fell into one of four main pathological

¹ [See paper in this number by R. R. Race (B.M.B. 872) —ED.]

groups—defects of development, asphyxia, intra-cranial haemorrhage, and infective diseases. A brief description of the principal pathological features of each of these is given. Mention is made of various less common conditions that

were included in the series, notably haemolytic disease of the foetus.

The importance of prematurity as a factor in neonatal mortality is emphasized.

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THE POST-MORTEM EXAMINATION OF THE NEWBORN INFANT

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The high mortality-rate of newborn infants is in striking contrast to the magnificent achievements of preventive medicine in reducing the mortality of later infancy. "The slight improvement in neonatal mortality in the last 30-40 years is due almost entirely to a reduction in the deaths in the last three weeks of the neonatal period" (Parsons, 1944). Any progress in this realm of medicine can be expected only from an accumulation of thorough knowledge of the physiology and pathology of intra-uterine life (Parsons, 1946), of the act of birth, and the transition from intra-uterine to extra-uterine life. The morbid anatomy of the neonatal period is an essential part of this science.

There is no unanimously accepted definition of the newborn infant. The frequently-adopted limit of 4 weeks is arbitrary. There are more differences between the pathology of the 1st week of life and that of the 3rd or 4th than between the latter and the 8th or 10th week. The first three months of extra-uterine life are on the other hand the most dangerous period of infancy, peculiar by the poor reaction to artificial feeding, low resistance to infections, and hydrolability. For this reason the designation "neonatal period" will be used in this paper as synonymous with the first three months of life, and the first week of life will be separated as the "early neonatal period".

A discussion of the pathology of the newborn infant is beyond the scope of a short article. The present paper will therefore be restricted to the description of a comparatively simple technique, which appears satisfactory to the writer, for the post-mortem examination of the newborn infant, drawing attention at the same time to frequent or interesting findings and their interpretation. We have, however, to realize that there is no post-mortem technique which can be dogmatically applied to every case. Each autopsy is a piece of individual research work, and the pathologist is often confronted with findings which demand a special technique.

I EXTERNAL EXAMINATION

The body should be inspected thoroughly for the presence of external abnormalities or injuries, cyanosis or icteric discoloration, abundance and distribution of lanugo hairs,

the configuration of the head, the direction of palpebra fissures, the presence of epicanthus, the ocular distance, the configuration of the small finger, the presence of oedema, scleroedema, sclerema or adiponecrosis subcutanea neonatorum.

The last three conditions are often confused. In scleroedema there is a hard pitting swelling of the skin and the impression of the finger disappears slowly. In sclerema, which is much rarer, the skin appears shrunken, is even harder, like wood, and pitting is absent or minimal. Adiponecrosis neonatorum is sometimes called scleroderma neonatorum or pseudo-sclerema. It is a sharply-demarcated local lesion of the skin, pale reddish or bluish in colour, traumatic in origin. Calcification and foreign-body giant-cells may be found on histological examination. Slight oedema is very frequent in the newborn infant. Marked oedema associated with pneumonia of the newborn has been repeatedly seen by the writer. Gross oedema associated with a large oedematous placenta should draw attention to hydrops foetalis, and the diagnosis should be checked by histological examination and serological tests on mother and baby. Post-mortem blood gives, however, reliable results in Rh tests only within a few hours after death.

The umbilicus and the skin deserve special attention. If the stump of the umbilical cord has fallen off and any exudate or membranes are present, these should be examined bacteriologically. In every case with trismus or tetanic cramps, the stump of the umbilical cord should be minced and ground with sterile Tyrode's solution or, in the absence of a stump, scrapings of the umbilical wound should be suspended in Tyrode's solution. A part of such a suspension should be used for anaerobic cultures, the remainder being injected subcutaneously into a mouse. "Stumps" more often give positive results for tetanus than "scrapings".

If large vesicles are present in the skin, or/and in large areas—especially on the face—the epidermis is separated from the corium, gentle pressure by the finger should be applied to an apparently normal area of the skin. An artificial separation of the epidermis (phenomenon of epidermolysis) is pathognomonic for Ritter's disease if the post-mortem examination is done shortly after death. Pustules and vesicles are the common form of skin infection in the early neonatal period, while deeper abscesses, so common in marasmic babies of later infancy, are rare at this age. The skin of the face should be inspected for the presence of diffuse syphilitic infiltrations and the "café au lait" colour, the lips for fissures, the palms of the hands and the plantar surfaces of the feet for diffuse desquamating infiltrations or syphilitic pemphigus. The latter is present at or appears immediately after birth and is seen only in the early neonatal period.

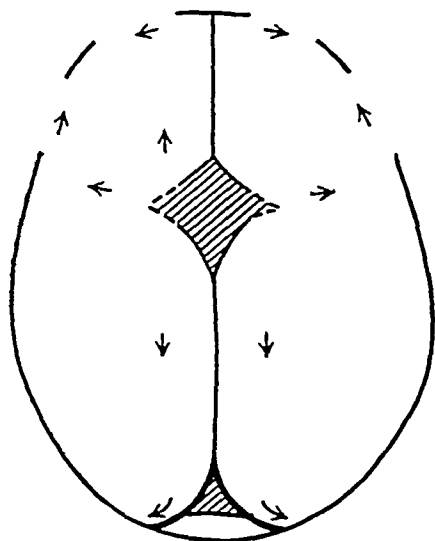
Before starting with the necropsy the mouth should always be inspected for the presence of Bednar's aphthae—

superficial ulcerations in the regions of the raphe palati and pterygoid processes—for thrush and for swelling of the alveolar processes. The latter, which is sometimes seen in young infants and may be associated with necrotic or gangrenous changes of the gingiva, is a septic process which is characteristic of the neonatal period. It was first described by Klementowsky (1876) as osteogingivitis gangraenosa, and its pathology was studied by Zarfl (1920). It is a haematogenous infection of the tooth-bud leading progressively to an osteomyelitis of the jaw, sequestration of the bud, and sometimes gangrene of the gingiva (Fischl, 1931).

II HEAD AND SPINAL CORD

The dissection of the head begins with the usual ear-to-ear incision, the two flaps being pulled forwards and backwards respectively and inspected for haemorrhages, serous or blood-stained fluid. The bones of the vault should then be examined for subperiosteal haematomata and fractures. The vertex of the brain is exposed without damage to the superior longitudinal sinus or the inflowing pial veins, by forming and turning down flaps consisting of the two parietal bones and the lateral halves of the frontal squama, according to the following technique: an incision is made with a pointed knife into the anterior fontanelle at its posterior margin, approximately 5 mm from the midline. The point of the knife is pushed parallel to the inner aspect of the parietal bone for 1-2 mm between dura and leptomeninges and the incision is extended to the lateral angle. In a similar way the opposite side and both anterior margins are incised. One blade of a pair of strong scissors is passed beneath the parietal dura at the medial end of the original incision and the parietal bone is cut longitudinally parallel to the sagittal suture and about 5 mm laterally to the latter. The incision is continued towards the lambdoid suture, and then laterally and downwards within the latter and finally in a similar way

FIG 1



Schematic drawing illustrating the technique for opening the skull of a newborn infant.
 - - - Primary incisions into the anterior fontanelle made with a pointed knife
 — Extensions made with a pair of strong scissors

in the coronal suture. The same procedure is applied to the other side and the two parieto-temporal flaps are turned outward. In the same way flaps of the two halves of the frontal squama are prepared and turned outward. It is usually necessary to make a horizontal fronto-medial extension with the help of a bone forceps, leaving only a short bridge for outward reflection of the flaps. The procedure, which leaves a medial strip approximately 1 cm in width with the intact superior longitudinal sinus, is illustrated schematically in Fig 1.

After reflecting the four flaps, the vertex of the brain, the terminations of pial veins into the superior longitudinal sinus, and—after a gentle sideward pushing of the hemispheres—the falx cerebri, can be easily inspected. Subdural haematomata over the vertex and rupture of pial veins close to their termination at the superior longitudinal sinus are not uncommon, especially in forceps delivery, and are due to kinking of the veins as a result of bitemporal compression and shifting of the parietal bones one over the other (Beneke, 1910). They may, however, occur in spontaneous delivery as a result of a disproportion between the size of the head and the width of the birth-canal. They are more common than is generally assumed, and they are by no means always fatal. Evidence for this statement is the frequent finding of haematogenous pigment on the interior aspect of the dura in later infancy. It is the writer's opinion that such not-immediately-fatal subdural haematomata are a frequent cause of feeding difficulties in the neonatal period. Their relationship to true pachymeningitis haemorrhagica interna, with parallel layers of spiderweb-like membranes, giant capillaries and accumulation of blood-stained or xanthochromic fluid, is a debatable problem.

Subarachnoid haemorrhages are the most common type of intracranial haemorrhage in immature babies, and are often associated with haemorrhagic oedema of the leptomeninges. Most of our knowledge concerning intracranial haemorrhages of immature infants is due to the work of Ylppo (1919, 1924).

After the vertex has been examined, the falx cerebri can be exposed by gentle sideways pushing of the cerebral hemispheres. Haematomata between the falx and the medial aspect of the hemispheres often accompany subdural haematomata over the vertex. Haematomata of varying size between the two dural layers of the falx are often found but, by themselves, without pathological significance. After inspection of the falx, the superior longitudinal sinus is opened and examined for thrombosis and post-mortem or terminal clots. Absence of clots in all sinuses of the dura mater, in the heart, and in the great vessels, associated with manifestations of haemorrhagic diathesis, is suggestive of congenital afibrinogenia (Allibone & Baar, 1943; Henderson, Donaldson & Scarborough, 1945). A definite diagnosis is, however, not permissible without knowledge of *intra vitam* laboratory findings. The possibility of post-mortem fibrinolysis or of asphyxia must be taken into account.

The next step in the examination is the separation of the falx at its antero-inferior insertion. This is then pulled backwards, the cerebral hemispheres are carefully pushed apart, and the corpus callosum is dissected longitudinally, exposing the superior tela chorioides. A preliminary inspection of the galenic veins is now made. Engorgement of these veins always suggests the presence of haemorrhages. A haematoma may be seen around one or both veins of Galen (vena cereo-

interna), and a rupture may be found near the point where they join the vena magna galeni. The frontal lobes are now raised, the olfactory tracts, the II-VI cranial nerves are cut transversally, and a horizontal cut is made through the pons varoli at the level of the incisura tentorii. The brain can then be removed, leaving the cerebellum, the medulla, and part of the pons in the posterior cranial fossa. The intact tentorium and the base of the skull are then inspected. Tentorial tears are caused by traction mainly due to bi-temporal or suboccipitobregmatic compression (Beneke, 1910, Holland, 1937). Clotted and unclotted blood may be found on the superior aspect of the tentorium and in the posterior cranial fossa. The main localization of tentorial tears is in the superior lamina. They are usually superficial, have ragged irregular margins, and can be easily overlooked. Fissures along the incisura tentorii are much rarer, but probably always fatal because of the massive haemorrhage into the posterior cranial fossa with compression of the medulla. The same is true for tears of the inferior lamina and those through both layers. Haematomata between the two laminae, varying in size from a lentil to a pea, are very frequent, and *per se* without pathological significance, like similar haematomata of the falx cerebri.

The tentorium is now incised along its insertion in the superior border of the petrous portion of the temporal bone, opening at the same time the superior petrosal sinus, and the incision is extended to the anterior part of the occipital insertion. The cranial nerves VII-XII are severed, the medulla is incised with a bistoury as deeply as possible, and the contents of the posterior cranial fossa are removed. The sinuses of the dura mater are opened and inspected, and the pituitary is removed without being touched by an instrument. This is done by making an arched incision along the anterior margin of the diaphragma sellae, grasping one of the posterior clinoid processes with a dented forceps, pushing the knife beneath the pituitary, and cutting through the cartilaginous dorsum sellae. The sella is inspected for remnants of the cranio-pharyngeal duct, which, if present, is found anteriorly, in or just behind the plane of the anterior clinoid processes. The dura of the middle cranial fossa is separated from the bone by means of a chisel and the middle ears are opened, the chisel being thoroughly clean and applied with as little inclination as possible. Slightly blood-stained serous or mucous exudate is very often (about 75%) found in the middle ears in the early neonatal period. This exudate is often sterile and is evidence of an aseptic foreign-body otitis media due to aspiration through the Eustachian tube. If the exudate becomes infected, a purulent otitis media may develop in the early days of life. The exudate is always present in the mastoid antrum as well as in the tympanic cavity. In rare instances the aspirated material contains tubercle bacilli, and this results in a primary tuberculous complex of the middle ear with extensive and uniform caseation of the lymph-nodes in the deep superior cervical group (Baar & Evans, 1941).

The sphenoid, maxillary and frontal sinuses, the ethmoidal cells, the nasal mucosa and the nasopharynx are inspected after a saw-cut in the coronal plane, approximately halfway between the sphenoid limbus and the ethmoidal spine. The angle of inclination of the clivus is measured, and the sphenoccipital and intersphenoid synchondroses are examined whenever a depression of the bridge of the nose is found

(achondroplasia, cretinism, etc.) The wings of the sphenoid should be examined when hypertelorism is suspected.

The brain previously removed is now examined further. The roof of the third ventricle is dissected, the pineal gland inspected, and a horizontal section with a brain knife is made through each cerebral hemisphere in such a way that the floors of the lateral ventricles are exposed.

The condition of the veins of Galen, the veins of the corpus striatum and choroid plexus, venae cerebri internae, venae terminales, venae ventriculi lateralis and plexus choroidei is of particular importance. They may be ruptured, and a gross intraventricular haemorrhage may be found, or they may be engorged with punctate haemorrhages in the grey matter surrounding the ventricles. Subependymal haemorrhages are often found on microscopical examination. The pathology of haemorrhages in the galenic system has been thoroughly studied and their mechanism elucidated in a fairly convincing manner by the classic work of Schwarz (1927) in Frankfurt.

According to Schwarz a suction-mechanism is responsible for the majority of intracranial haemorrhages. As soon as the head exchanges the high intra-uterine pressure for the lower atmospheric pressure, a negative pressure is applied to it causing not only a caput succedaneum but also intracranial haemorrhages by propagation through the less-resistant parts of the skull to the sinuses of the dura mater, in particular to the sinus rectus and then to the vena magna Galeni and its tributaries in the galenic system ("caisson mechanism"). A similar mechanism may operate in breech deliveries as a result of rapidly-changing intra-uterine pressure. Schwarz's work has been challenged by some authors, and certainly his ideas are somewhat one-sided. For instance, engorgement and rupture of the veins of Galen may be due in some cases to their being kinked (Holland, 1937), asphyxial haemorrhages are often indistinguishable from those by suction-mechanism, and micronecroses and Virchow's "encephalitis interstitialis neonatorum" (1867) may result not only from birth injury but also from septic infections and from kernicterus (Ceelen, 1920, Baar, 1937). Moreover, physiological reflexes of the newborn, hypertonicity and extensor plantar reflexes, which Schwarz attributed to intracranial haemorrhages, are more reasonably explained by the immaturity of the central nervous system (Reuss, 1931).

Nevertheless, for the majority of cases, the theory of Schwarz appears to the writer to be correct. His theory is supported by the engorgement involving the vena magna galeni and the sinus rectus, by the association with caput succedaneum, by the association of subependymal haemorrhages with clusters of compound granule cells in areas of rarefaction and with perivascular crescents. Intracranial haemorrhage and traumatic necrosis are also responsible for the majority of cases of encephaloclastic porencephaly (Jakovlev, 1941) (=pseudoporencephaly=central porencephaly=cystic degeneration of brain) (Benda, 1945), and of Vogt's status marmoratus of basal ganglia. Encephaloclastic porencephaly is much more common than true developmental porencephaly (Fig 3).

At this stage of the post-mortem examination, kernicterus can often be diagnosed. The beautiful golden-yellow spotty discoloration of the thalamus and corpus striatum, especially of the circular cut surface of the tail of the caudate nucleus, are striking findings. These are, however, not the most

frequent localizations Kernicterus may be present without discoloration of the thalamus and corpus striatum. The examination of the nucleus ruber, corpus luyssi and inferior olives is, however, better postponed until the brain has been properly fixed, otherwise no satisfactory histological examination can be performed. It is also worth mentioning that removal of any blood from the cut surfaces of the brain should be done with a clean dry knife, and never with running water. The latter procedure produces marked changes in the nerve cells, and the demonstration of intracellular neurofibrils is rendered impossible (Nissl's "Wasserschaden"). After 3-4 days' fixation the brain is dissected by coronal sections into a series of slices about 5 mm. in thickness. The important nucleus ruber is best seen in the section just anteriorly to the superior corpora quadrigemina. Material should always be set aside for paraffin and for frozen sections. Fixation of the whole brain before any dissection has been performed is often advisable, while injection of formol saline into the internal carotid 12-24 hours before the post-mortem examination is only exceptionally justified in the neonatal period.

Kernicterus is in the vast majority of cases due to icterus gravis neonatorum. Three cases of kernicterus without haemolytic disease, reported in the pre-Rh era, have been recently questioned (Gilmour, 1944). The writer saw one case of kernicterus in which haemolytic disease of the newborn was excluded by haematological and serological investigations. In addition, in one case with haemorrhagic necroses of the liver, histological changes were found in the brain of the same type as in kernicterus. From these observations, based on the histological study of a dozen cases with kernicterus and haematological findings, the conclusion was reached that kernicterus is a hepatogenic encephalopathy, the hepatic disease being in most cases the result of the action of Rh antibodies on the cellular antigens of the liver (Baar, 1945).

Virchow's encephalitis interstitialis neonatorum is a fairly common finding in brains of newborn infants. It is not a distinct pathogenic entity, as it is found in birth-injury, in septic infections, and in haemolytic disease of the newborn. It is usually recognized on histological examination only. Sometimes, however, a peculiar greyish-red colour is noticed in the white matter, which Virchow compared with that of hortensia. Histologically, the most marked changes are found beneath the ependyma of the posterior horns of the lateral ventricles. A perivascular crescent in a case of "encephalitis interstitialis neonatorum" is seen in Fig. 4.

Purulent leptomeningitis is not uncommon in the neonatal period. It is usually caused by *B. coli*, more rarely by *Klebsilla friedländeri* (*Bacillus mucosa*). Unusual strains of *B. coli* as causative organism of leptomeningitis were found at the Children's Hospital, Birmingham, on two occasions, once a *B. coli anaerogenes* which was positive by the methyl-red and Voges-Proskauer tests, and once a strain which resembled biochemically *E. freundii*. Associated with purulent leptomeningitis or without it, there may be found a septic encephalitis which usually takes a necrotizing-haemorrhagic form, abscess formation being rare.

For the findings in the rare *Toxoplasma* encephalitis of newborn infants, the monograph of Sabin (1942) should be consulted. An infective encephalitis of the newborn resembling toxoplasmosis with coarse subependymal granulations (Fig. 5) has recently been described by Parsons & Baar (1945).

The spinal cord is often neglected in the post-mortem examination of the newborn baby. It is easily exposed by using bone forceps. When being removed it should be held by the cauda equina or the terminal end of the dura without being touched during the whole procedure. Epidural haematoma are found mainly in immature infants, subdural and cord haemorrhages in full-term infants.

III NECK, THORAX, AND ABDOMEN

For the dissection of the neck, the thoracic and abdominal organs, only the "en masse" technique, after thorough inspection *in situ*, is advisable. The following is a slight modification and combination of directions given by Virchow, Rokutansky, Ghon and Rossle. An antero-median incision is made from the middle of the neck down to the symphysis pubis passing to the left of the umbilicus. After the abdominal cavity has been opened in the whole length of the incision, the skin is separated from the deeper structures of the neck and the thoracic wall, exposing the ribs and costochondral junctions with their periosteum and perichondrium intact. The peritoneum is now inspected and samples of any exudate present are taken for bacteriological examination. The umbilical vein and arteries are examined, the first by a longitudinal slit with small scissors, the latter by a series of cross-sections. Umbilical infection, one of the most important sources of neonatal sepsis, may be present without obvious external involvement of the umbilicus. Macroscopically-recognizable thrombophlebitis umbilicalis is rare, although it may be revealed by histological examination (Morrison, 1944). Umbilical arteries may show a purulent periarteritis, thrombarteritis or a combination of both, the first being in the writer's experience the most frequent.

The gastro-intestinal tract is examined by inspection and palpation for the presence of malrotation, free common mesentery, atresias, the presence of Meckel's diverticulum or persisting vitelline duct, diaphragmatic hernia, *intra vitam* or terminal intussusception, etc. Palpation of the pylorus is very important. A hard hypertrophic pylorus may be found in the early neonatal period before any clinical symptoms have arisen. Dilatation of the duodenum indicates a duodenal stenosis, and is in the majority of cases due either to true obliteration (infrapapillary more often than suprapapillary) or to a torsion as a result of a persisting common mesentery. The latter condition is almost always associated with some malrotation of the gut. Stenoses due to peritoneal bands or abnormal blood-vessels are rare. Multiple atresias of the intestine are not uncommon and usually associated with wedge-shaped defects of the mesentery. After this inspection a decision whether the intestine should be removed separately or included in the "en masse" removal can be made. The latter procedure is always indicated in the presence of atresia ani for the investigation of recto-vaginal, recto-urethral or recto-vesical fistulae, and also in the presence of a thrombosis of mesenteric veins. If the former procedure is decided, the transverse mesocolon is dissected first along its posterior insertion, the descending colon is separated from the abdominal wall, the sigmoid mesocolon is dissected, the rectum freed, transected at the anus and lifted upwards. The dissection is continued downwards from the flexura hepatica separating ascending colon and caecum or cutting through their mesocolon if such be present. The whole intestine is now lifted and the mesentery of the small intestine is divided with scissors from the ileo-caecal junction medial and upwards.

towards the flexura duodeno-jejunalis. The upper end of the jejunum is twice ligated and cut between the ligatures. The sternum is removed by cutting with a cartilage-knife on each side approximately midway between the sternum and the costochondral junctions from the second rib downwards, continuing the incision in an arched way towards the costal margin. The diaphragm is incised and the sternum is separated from the areolar tissue of the anterior mediastinum by raising the xyphoid end of the sternum and dissecting upwards with a knife as close to the bone as possible. The cartilages of the first ribs are divided and the sternum is finally freed by passing the blade of the knife through the sterno-clavicular articulations. The pleural cavities are inspected and samples of any exudate are taken for bacteriological examination. A fibrino-purulent exudate on the pulmonary pleura is often found, but larger amounts of free exudate are less common. Any free exudate is usually a thin, turbid, slightly blood-stained fluid. Creamy pus is rarely met with in the early neonatal period. Pleural infections are in newborn infants, as at a later age, almost invariably secondary to a pulmonary involvement. There is, however, evidence of an occasional haematogenous infection of the pleura with secondary involvement of the subpleural lymph-vessels and lung parenchyma (Macgregor, 1939).

The tissues of the neck are now extensively exposed by passing the knife in a lateral direction between the skin and the deeper structures. The sternocleidomastoid muscle is thoroughly examined for the presence of injury. If fibrous tissue is seen within the muscle, a piece is taken and histologically examined for haemosiderin. If a swelling of the parotid was noticed on external examination the gland can be approached from the incision in the neck and slices can be taken for histological and bacteriological examination. A purulent parotitis is not uncommonly the first, or even the only, manifestation of a septic infection in the newborn. It may perforate into the external auditory meatus.

A pointed knife is now passed upwards in the midline between the tongue and the mandible, close to the latter. The incision is extended laterally and backwards along the arch of the mandible and close to the latter down to within a few millimetres of the angle. After this procedure has been carried out on both sides the tongue is pulled forwards and downwards beneath the mandible with the aid of forceps. A pointed knife is inserted in the midline between the hard and soft palate, an arched incision is made between these two structures and extended sideways and downwards into the wall of the pharynx and the soft tissues of the neck, always keeping as far laterally as possible.

This incision being completed on both sides, the knife is placed between the posterior wall of the pharynx and the spine, the pharynx and the upper part of the oesophagus are separated from the latter and pulled downwards and forwards, leaving the main muscles of the neck and the large blood-vessels in the body. Each lung in succession is extorted anteriorly and medially, the dome of the pleura is incised, and the blood-vessels of the neck are severed as high as possible. The tongue, with the pharynx and larynx, are now firmly seized by the right hand and pulled vigorously downwards, thus separating all thoracic organs down to the diaphragm. Only exceptionally are there such pleural adhesions that separation with the help of a knife is necessary.

The spleen is shifted by the left hand away from the ribs, and the diaphragm is incised along its insertion. A similar

procedure is carried out on the right side between the liver and the ribs. All abdominal organs together are separated from the posterior abdominal wall, and the dissection is continued along the wall of the pelvis. Finally, the symphysis is severed with a cartilage knife, the urethra or vagina is severed and the incision is extended backwards and the organs are finally freed and taken out of the body. If, however, inspection revealed evidence of malformation of the urinary tract, the necessary dissection is in the male somewhat laborious, in order to avoid external mutilation. The prostatic part of the urethra is exposed, held with a forceps, traction is exerted, and the urethra with corpus spongiosum, corpora cavernosa and glans penis are removed by careful dissection, leaving the skin intact. The skin can subsequently be packed with cotton wool.

The seventh rib is cut with a cartilage knife longitudinally and perpendicularly to its surface, a slice of about 1-2 mm in thickness is removed, and the costochondral junction is inspected for the presence of osteochondritis syphilitica. The latter is suggested by a broadening and irregularity of the provisional calcification zone, which is also more yellow and brittle than normal. Softening, greyish discoloration, grey or yellow areas of soft tissue in the subepiphyseal zone, due to proliferation of syphilitic granulation tissue, may be found in more advanced cases. One should never be satisfied with a negative finding in the ribs, but the lower end of the femur should also be examined. Syphilitic osteochondritis of the newborn may be associated with juxta-epiphyseal periostitis and epiphyseal separation may also be found, but confusion with artifacts from sawing has to be avoided. To avoid this confusion L. Pick (1929) recommends the use of an electric "band saw" after freezing of the bone. In the early neonatal period syphilitic osteochondritis is always associated with visceral syphilis. Rickets is not found before the third month of life in full-term infants, or before the end of the second month in immature babies. Congenital rickets has, however, been described by Maxwell, Hu & Turnbull (1932) in Chinese babies of osteomalacic mothers. Early rickets can be recognized on histological examination only, and partial decalcification with Muller's fluid is very useful for the demonstration of osteoid borders.

IV EXAMINATION OF VISCERA

The examination of the organs removed "en masse" is now undertaken. The soft palate is cut through in the midline, the pharynx, the epiglottis and the tonsils are inspected, and incisions are made into the latter. Although rare, purulent tonsillitis may be found in the neonatal period. All organs are placed on a board in such a way that the pathologist faces their posterior aspect. The aorta is severed above the diaphragm and its posterior wall is incised longitudinally, extending the incision into the left subclavian artery. Any blood is removed, the aorta is washed with running water and inspected. Attention is to be paid to any icteric discoloration of the intima, to the orifice of the ductus arteriosus, and to the presence or absence of a coarctation of the aorta, which is usually situated in the level just above or just below this orifice (isthmus stenosis).

Although circulation in the ductus arteriosus ceases almost immediately after birth (Barclay, Barcroft, Barron & Franklin, 1938, 1939), the anatomical obliteration is a slow process usually commencing at the pulmonary end, and in the majority of cases it is not completed until the end of the second

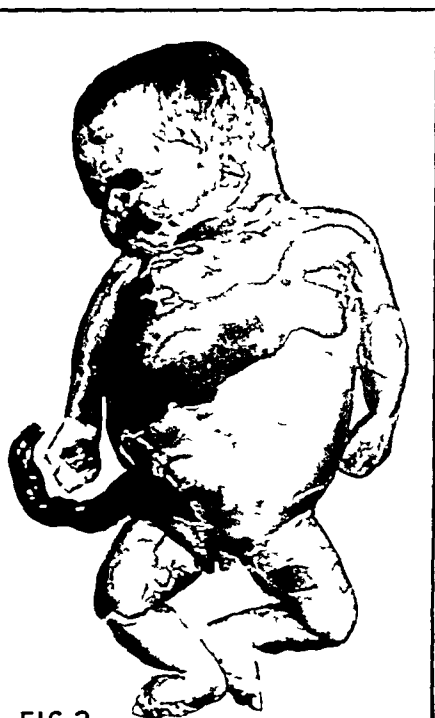
POST-MORTEM APPEARANCES IN THE NEWBORN

(FIGS 2-14)

H S Baar

- 2. Macerated foetus with hydrops foetalis

FIG 2

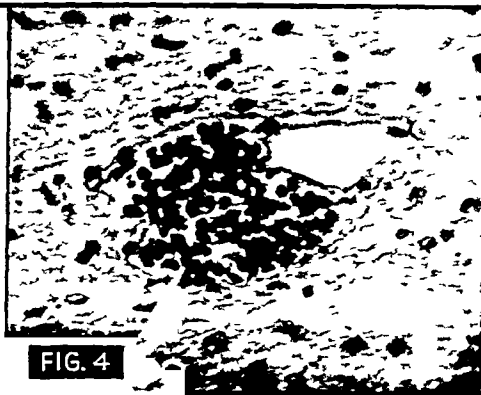


- 3 Encephaloclastic porencephaly
- 4 Perivascular crescent in Virchow's Encephalitis interstitialis neonatorum

FIG 3



FIG 4

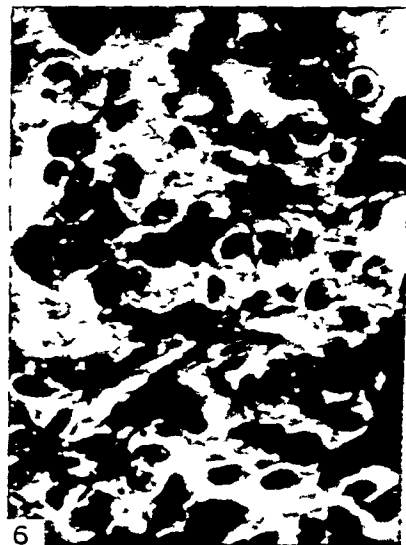


- 5 Coarse subependymal granulations in a case of infective encephalitis of the newborn resembling toxoplasmosis

FIG 5



FIG 6



- 6 Initial atelectasis of the newborn

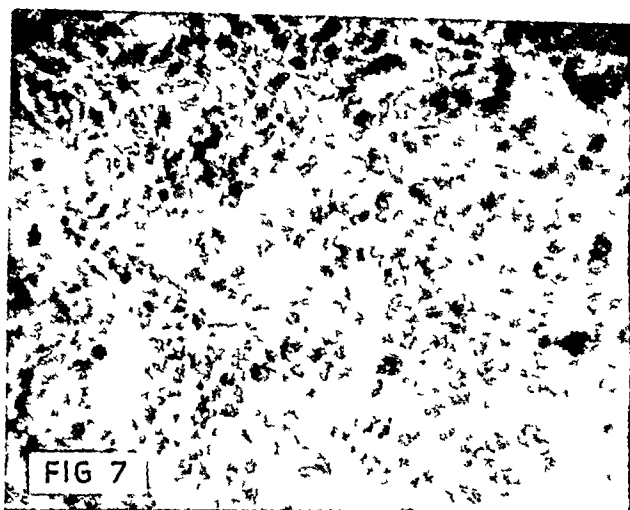


FIG 7



FIG 8



FIG 9

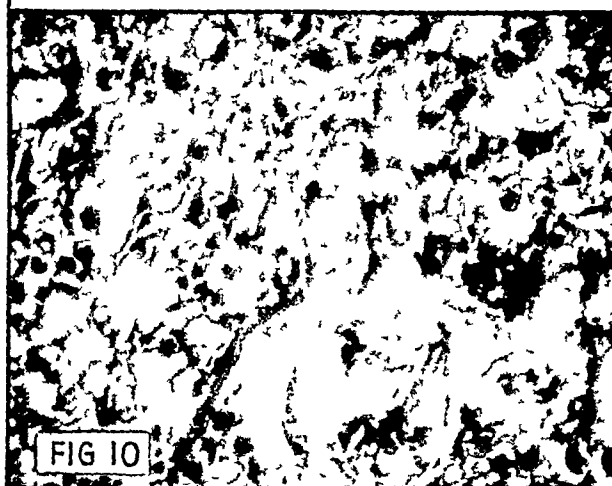


FIG 10

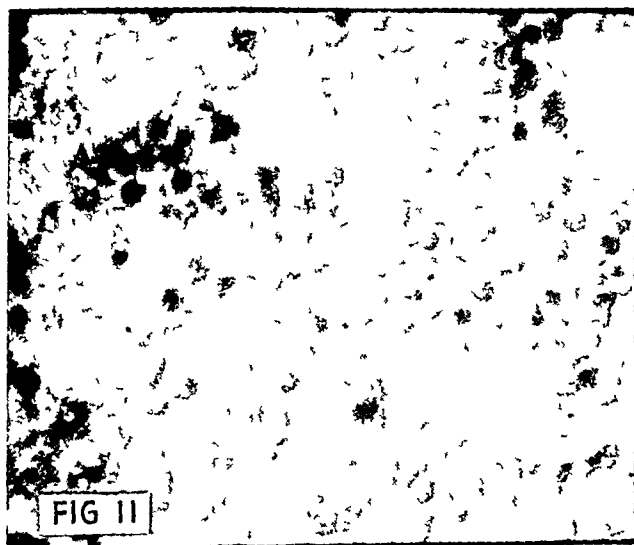


FIG 11

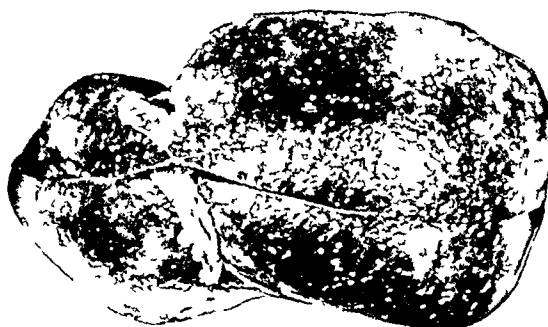


FIG 12

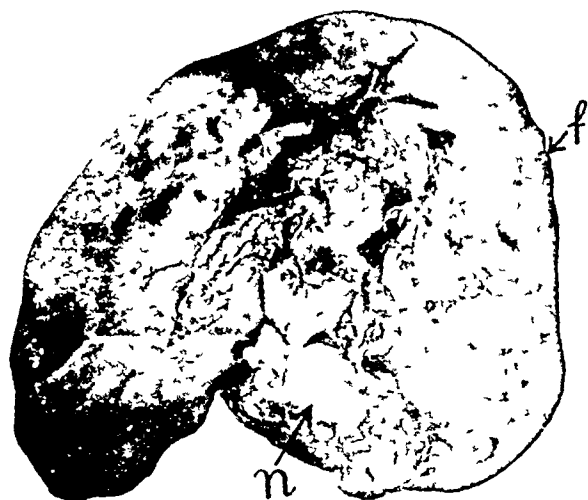


FIG 14

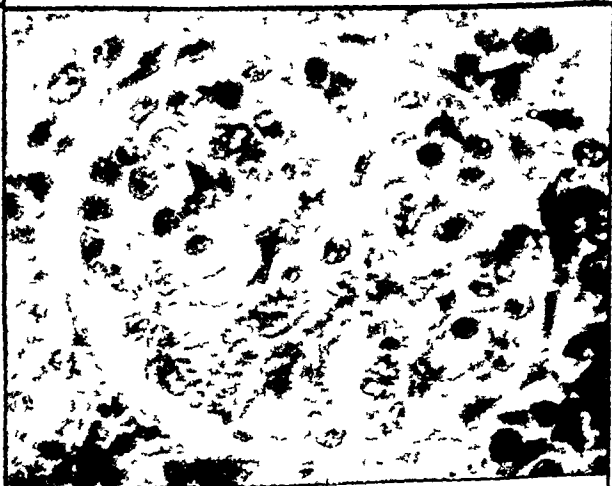


FIG 7 "Resorptive atelectasis" of the newborn

FIG 8 Squamous cornified epithelia cells and meconium body (M) in a bronchus of a stillborn infant

FIG 9 "Vernix membrane" in a small bronchus of a newborn infant

FIG 10 Squamous epithelial cells and vernix membranes in an alveolar duct of a newborn infant

FIG 11 Haematopoiesis in the liver of an immature infant (seven months gestation) The baby died 15 minutes after birth The cause of death was an intrapericardial teratoid neoplasm

FIG 12 Non syphilitic miliary necroses of the liver in a six weeks old infant

FIG 13 Primary tuberculous complex in the liver in a case of congenital transplacental tuberculosis
f = primary focus
n = caseated lymph nodes at porta hepatis

FIG 14 Bloodless, partly hyaline glomerulus in kidney of newborn infant

month of life. A partial anatomical obliteration is often present at the age of 3-4 weeks, and the central part may remain open for a long time after the pulmonary and aortic ends are obliterated (Jager & Wollenman, 1942). Monckeberg (1924) accepts a patent ductus arteriosus as pathological only if it is found after the age of three months. Probing of the duct should be postponed until the heart has been dissected, and is carried out from the pulmonary orifice which is seen just above the division into the right and left branches.

The proximal part of the aorta should be inspected for an anomalous right subclavian artery (arising from the descending aorta and turning upwards and to the right side behind or before the oesophagus—dysphagia lusoria) and for an aberrant ductus arteriosus (very rare). The aorta is separated from the oesophagus and turned over the left main bronchus in front of the left lung. The oesophagus is inspected. A saccular dilatation of its upper part indicates the presence of an atresia, in the common form the upper part forms a wide blind sac, while the lower part is normal in width and communicates with the trachea just above the bifurcation by a narrow fistula. In such a case each part separately is cut longitudinally and a probe is passed from the opening at the proximal end of the lower part into the trachea and larynx to demonstrate the presence of a fistula. Other forms of oesophageal atresia are very rare. If nothing abnormal is seen on external examination of the oesophagus, it is slit along its posterior wall from the pharynx downwards.

White patches the size of a pin's head or, by their confluence, white membranes of thrush, which are firmly adherent to the oesophageal wall, are very common in newborn infants. The writer does not agree with the view, which has gained ground in recent years, that the thrush produces inflammatory changes, but he believes that it is a saprophyte growing readily on tissues either damaged mechanically or chemically (HCl of gastric juice) or reduced in their vitality by marasmus.

The oesophagus is carefully separated from the trachea, after having been severed above the diaphragm, with the help of scissors, leaving the paratracheal lymph-nodes and parathyroids *in situ*. The lower parathyroids are exposed by following the inferior thyroid artery, the upper by careful dissection of the tissues between the oesophagus and the thyroid. There is much variation in the number and the situation of the parathyroids, and they may be embedded in the thyroid or, in the case of the upper ones, in the thymus. Microscopical haemorrhages and later pigmentation are very frequent in infantile parathyroids. In the postneonatal period, pigmentation is found as frequently in normal infants as in those with tetany, and there is no relationship between parathyroid haemorrhage of the newborn and tetany of later infancy. The rare tetany of the newborn, however, may be occasionally caused by massive haemorrhagic destruction of parathyroids (Tezner, 1927, Baar, 1937). The thyroid is inspected and incised. Severe congestion of the thyroid is common in asphyxia of the newborn. Congenital goitre is common in such countries as Styria, and may be occasionally the cause of suffocation. Complete absence of the thyroid (thyreoaplasia) is the common cause of congenital myxoedema.

Respiratory Organs and Thymus

After examination of the tracheo-bronchial lymph-nodes, the trachea is slit along its posterior wall and the incision is extended into the main bronchi. Large amounts of fluid,

mucus, or muco-purulent exudate, may be found in the trachea, which should be examined microscopically for elements of liquor amnii. The problem of aspiration of amniotic fluid as evidence of intra-uterine asphyxia has been elucidated by the work of Johnson & Meyer (1925), Farber & Sweet (1931), and Macgregor (1939). As early as the sixteenth century, Vesalius observed that disturbance of the placental circulation in an animal foetus brought about definite respiratory movements resulting in aspiration of liquor amnii. This problem, about which there was much controversy, has been clarified by the admirable work of Barcroft (1942). Some intra-uterine respiratory movements appear to be physiological (Patterson & Farr, 1939), but the writer agrees with Macgregor that large amounts of aspirated liquor amnii are always evidence of intra-uterine asphyxia. The resulting inflammatory changes in the bronchial tree and in the pulmonary parenchyma may be bacterial, due to irritative action of vernix caseosa, and thus comparable with the "physiological" foreign-body otitis media of the newborn. Large amounts of amniotic fluid may prevent expansion of the lungs, and accumulation of mucus as a result of irritation may produce a secondary obstruction.

The inspection of the pleurae frequently reveals pin-head-sized, sometimes hempseed- to lentil-sized [2-4 mm], subpleural haemorrhages. In the examination of the lungs, which are incised by any of the routine methods, there are great difficulties in the differentiation of atelectasis, pneumonia and massive haemorrhage, and a final opinion should be given only after histological examination. Atelectatic lungs are purplish-red in colour and fleshy in consistency, contrasting with the pale pink aerated areas which are mainly localized in the anterior parts of upper lobes. In the presence of aerated areas in the lungs of still-born infants, the possibility of artificial respiration has always to be taken into account. Diffuse pneumonic changes can easily be confused with collapsed parenchyma, but patchy pneumonic areas are often felt as areas of firmer consistency even in collapsed lungs, and may be seen to project slightly on the cut surface. Massive haemorrhage and haemorrhagic pneumonia are very similar on palpation and macroscopic examination. The former, however, is usually more extensive, but it should be remembered that pneumonic changes occur often secondarily in areas of massive haemorrhage. Histological examination will usually enable the distinction to be made. Interstitial emphysema, sometimes very marked in newborn infants, is always evidence of inflammatory changes or of obstruction, being the result of alveolar rupture. Histological examination of the lungs of newborn infants reveals a surprising frequency of inflammatory changes. Microscopical examination is also necessary to differentiate "initial" from "resorptive" atelectasis, and for the demonstration of anatomical immaturity of lungs (Farber & Wilson, 1933, Wilson & Farber 1933). Lungs with initial atelectasis show a "glandular" appearance, with tubules of cubical epithelium lining a slit-like lumen, in contradistinction to resorptive atelectasis, where the lining is a flattened epithelium. If the initial atelectasis is incomplete (partial aeration) the lumen is wider and more saccular in shape, but the lining is still cubical. Atelectasis, especially resorptive, is always associated with engorgement of the capillaries of interalveolar septa (Fig. 6, 7). In the lungs of immature infants clusters or masses of cells resembling alveolar epithelia are seen without a trace of a lumen (unexpandable areas, Farber & Wilson, 1933).

Pneumonia of the newborn may be due to aspiration of amniotic fluid, aspiration of vomited material, aerogenous and haematogenous infection. The first type is the most interesting. Cornified squamous epithelial cells are found in the bronchi, bronchioli and air sacs. They appear as wavy lines or as cells, dome-shaped in the centre and tapering towards both sides. Nuclei are usually absent. Lanugo hairs may also be seen, and occasionally particles of meconium recognizable as a yellowish amorphous mass or as greenish-yellow spherical or ovoid bodies—Huber's meconium bodies. A characteristic feature, though not always present, is the "hyaline membrane" (Johnson & Meyer, 1925) or "vernix membrane" (Farber & Sweet, 1931). This is a homogenous membrane, pink or bright red in haematoxylin-eosin stained sections, lining the bronchioli and alveoli. It resembles the hyaline membrane in influenza (Wolfbach, 1919), but squamous epithelial cells may be seen within the membrane, and Sudan stain reveals the presence of fatty material while fibrin is absent. It results from elements of the vernix caseosa being flattened by the entering air or fluid against the walls. Such findings may be met with in the absence of pneumonia, or inflammatory cells may be present in the alveoli (Fig 8, 9, 10).

Haemorrhagic pneumonia is very frequent in the neonatal period. It often results from aspiration, postnatal more frequently than intra-uterine. If the necropsy is made some time after death, pneumonic areas from aspiration of vomited material may assume a brownish colour due to the formation of acid haematin from haemoglobin. Such areas are not to be confused with the soft "digested" brown areas due to post-mortem changes in uninflamed areas after terminal aspiration of gastric contents.

Aerogenous pneumonia is associated with exudative bronchitis and cellular alveolar exudate. Mural bronchitis and peribronchitis are moderate or absent. The main localization of aerogenous pneumonia in newborn infants, as in later infancy, is in the postero-inferior part of the right upper lobe, the part of the lung which has physiologically the poorest aeration. In marasmic infants of the later neonatal period, paravertebral pneumonia is often found. This forms thin subpleural strips of consolidated parenchyma in the posterior paravertebral parts of both lungs. It extends usually only a few millimetres beneath the pleura, and the differentiation from collapse in these areas is often difficult.

Septic haematogenous infection of the lungs results in septic haemorrhagic infarcts, in an infarct pneumonia, sometimes in multiple, small, symmetrical abscesses. The septic haemorrhagic infarcts may resemble aseptic infarcts, but there is usually a narrow yellowish demarcation zone. Empyema of the pleural cavity or fibrino-purulent pleurisy is always present in pyaemic infections of the lungs. Purulent pleurisy of the left side is often associated with fibrino-purulent or fibrinous perisplenitis. Pneumonia of the newborn is sometimes caused by *B coli*. This type of infection occurs only in the neonatal period (Macgregor, 1939), but care is needed in the interpretation of bacteriological post-mortem findings, because of the possibility of post-mortem invasion of the blood-stream and the tissues from the intestine. Direct smears and their correlation with cultural findings are indispensable.

Tuberculous infection of the lungs is only exceptionally met with in the neonatal period, but congenital transplacental tuberculosis with a typical primary complex in the liver

(Fig 13) may be associated with a simultaneous infection of lungs via the ductus venosus, and results in the formation of a (usually progressive and cavitating) pulmonary complex in addition to that in the liver.

A primary inhalation tuberculosis is only exceptionally discovered in the post-mortem examination of newborn infants in the absence of caseation. The early primary focus may resemble an unspecific consolidation, although usually it is more sharply demarcated. Histological examination reveals a mononuclear infiltration of the interalveolar septa, and mononuclear exudate in the alveoli with acid- and alcohol-fast bacilli (Pagel & Price, 1943). Exceptionally, the exudate is polymorphonuclear or shows microscopical caseation (Zarfl, 1912, Beitzke, 1930). Such lesions are likely to remain unrecognized unless attention has been drawn to such a possibility by the clinical history.

Syphilitic pneumonia alba is extremely rare in live-born infants, but not uncommon in syphilitic still-births.

The anterior mediastinum and the thymus are inspected and the latter is incised for the presence of "Dubois' abscesses". Hyperplasia of the thymus is more often diagnosed than really present. Weights up to 20 and probably 25 g should be considered as normal in the neonatal period. A definite hyperplasia of the thymus, associated with general hyperplasia of the lymphadenoid tissue, is evidence of an abnormal constitution, but is never the cause of death, and the existence of a thymic stridor or thymic asthma is not supported by post-mortem examinations.

Heart, Pericardium, and Vessels

The pericardial sac is opened and the pericardium, epicardium, heart, aorta and pulmonary artery are thoroughly inspected. Subepicardial haemorrhages, "taches du Tardieu," are not pathognomonic of asphyxia, since punctate subepicardial haemorrhages also occur in septic conditions and in haemolytic and haemorrhagic disease of the newborn. Streak-like subepicardial and myocardial haemorrhages are, however, very suggestive of asphyxia. Fibrino-purulent pericarditis associated with mediastinitis is occasionally seen in the later neonatal period as a sequel of purulent pleurisy. The size of the heart in a newborn infant, as later, is approximately that of its clenched fist.

The necessity for special technique in the examination of each organ applies particularly to the heart. Especially in the various forms of transposition of great vessels, the most suitable technique has to be considered thoroughly before starting with the dissection. The discussion of the pathology of congenital heart disease is beyond the scope of the present paper, and the monograph and atlas of Abbott (1927, 1936), the monograph of Monckeberg (1924), and the papers of Spitzer (1923) and of Harris & Farber (1939) should be consulted for this purpose.

If there appears to be no necessity for a special technique, Rokitsky's method, slightly modified, has proved most satisfactory. In this method the heart is grasped with the left hand around its right border, an incision is made with a pointed knife into the lower end of the left border of the left ventricle, the ventricle is opened and all clots are removed. The knife is then passed through the mitral orifice to the point where the left pulmonary veins join the left ventricle, and the incision is extended, thus exposing the left ventricle and auricle. Further clots are removed, the chambers are washed with running water, and gently dried with a sponge.

The chambers and the mitral valve can now be inspected. Tiny blackish nodules in the mitral valve, the so-called valvular haematoma or valvular angiomata, are not uncommon in the neonatal period. They are remnants of the embryonic vascularization of the valve, and are without pathological significance. The heart is now grasped with the left hand around the left ventricle, and an incision is made into the right border of the right ventricle. With the help of long scissors this incision is extended into the superior vena cava.

After having been cleaned, the chambers of the right side and the tricuspid valve can be inspected. Thin threads in the right auricle, "the network of Chiari," are a developmental abnormality without pathological significance. The foramen ovale shows in the majority of cases a valvular patency only. A crescentic patency in the antero-inferior part 1-2 mm. in width is, however, within the limits of normal. In determining whether the patency is pathological or not, the presence of an enlargement of the heart is more important than the size of the opening.

The heart is now placed in such a way that the pathologist faces the pulmonary artery. Scissors are passed into the artery and an incision is made along its left (really anterior) margin. The pulmonary conus, valve and artery are inspected, and if necessary a probe is passed into the ductus arteriosus. The aorta is next examined by passing the scissors behind the anterior cusp of the mitral valve, so that in opening the aorta the pulmonary artery is cut just above its valve. The three cusps of the aortic valve are now seen—the anterior in the middle, the right and left with their coronary ostia on each side. A bicuspid aortic valve is not a very uncommon finding. Such a valve has to be examined histologically to decide whether the condition is developmental or inflammatory. Special attention is to be paid to the pars membranacea of the interventricular septum, where patency is comparatively frequent. Large or small openings may be found in any part of the interventricular septum, those at the lower end being often small and easily overlooked. It would be erroneous to consider every heart disease in a newborn infant as a developmental error, because foetal endocarditis, although rare, certainly does occur. A marked hypertrophy without developmental errors or foetal endocarditis is very suggestive of cardiomegalia glycogenica, which may occur without glycogen storage in the liver. In such case, a piece of tissue is taken for quantitative glycogen estimation and another to be fixed in Lison's (1936) modification of Bouin's fluid (8.5 cm³ dioxane saturated with picric acid, 1 cm³ concentrated formaldehyde solution, 0.5 cm³ glacial acetic acid) for Best's carmine stain. Sometimes a hypertrophy of the heart of obscure origin is encountered in the neonatal period, the so-called idiopathic hypertrophy of the heart in the newborn, and rarely an enlargement of the heart is due to a rhabdomyoma.

Stomach, Liver and Bile-ducts, Spleen

The examination of the abdominal organs is started with the opening of the stomach by an incision in the anterior wall parallel to the greater curvature, the incision is extended into the duodenum. Peptic gastric or duodenal ulcers occur in the early neonatal period and in marasmic babies in later infancy, and may be the cause of melaena neonatorum. The pylorus in congenital hypertrophic pyloric stenosis is hard,

feels like cartilage, and shows a marked thickening of the wall, the hypertrophic muscular coat being conspicuous by its greyish-white colour. The normal thickness of the pyloric wall is 1.5-2 mm. In pyloric stenosis it is usually 3.5-7 mm. The figure 3.5 mm. as the upper limit of the normal given by some authors is, in the writer's experience, too high. A hypertrophy of the body of the stomach was seen by the writer in three cases of pyloric stenosis.

The patency of bile ducts is examined by manual pressure on the gall bladder and by probing common bile-duct from the papilla of Vater. A probe can also be passed into the pancreatic duct, but this procedure is not advisable because, in normal infants, a thin probe can be passed only for a short distance, and the duct is damaged, thus making the interpretation of histological findings difficult. If fibrocystic disease of the pancreas is suspected, conclusive information about the condition of the ducts can be obtained only from serial sections. In this disease, the pancreas may be harder than normal. The normal pancreas of young infants is much softer than that of older children. Only exceptionally an abnormal structure may be noticed on section in naked-eye examination, and in the majority of cases fibrocystic disease of the pancreas is discovered only on histological examination. It should be suspected in all cases of meconium ileus (*vide infra*), or obliteration of the small intestine. Among 38 cases of cystic fibrosis of the pancreas studied at the Children's Hospital, Birmingham, there were 7 cases in the early neonatal period, 4 being associated with meconium ileus, one with suprapapillary and one with intrapapillary duodenal atresia, and one with atresia of the lower ileum. The association with bronchiectases, suppurating pneumonia and peribronchial abscesses, which is common in later infancy, does not occur in the early neonatal period.

Only a few of the numerous pathological conditions of the liver seen in newborn infants can be mentioned. In congenital obliteration of bile ducts, the liver is enlarged, dark green and hard, its surface being either smooth or finely granular. The cut surface shows green dots separated by strands and spots of grey tissue, the strands forming a network in many places, and a similar appearance may be found without obliteration of extrahepatic bile-ducts (Parsons & Hickmans, 1926). Infective biliary cirrhosis (Rössle's cholangitic biliary cirrhosis) is not rare in the neonatal period. On histological examination it usually does not present the features of a pure "perilobular" cirrhosis, but shows a marked ingrowth of fibrous tissue into the individual lobuli. In infants surviving for a longer period, a distortion of the hepatic structure may be found comparable only with that seen in syphilitic hepatitis. Biliary cirrhosis may also be found as a sequel of icterus gravis neonatorum in infants surviving for some weeks. In infants with icterus gravis dying in the first days of life, the liver is either green or reddish brown, moderately firm, and on section the lobular structure is indistinct or not discernible, Perl's reaction is strongly positive. On histological examination in all cases of haemolytic disease of the newborn the liver shows, all over the section, dilated capillaries packed with nucleated erythrocytes. In livers of normal full-term babies, only an occasional haematopoietic focus is seen, but the liver of an immature infant dying in the early neonatal period may be indistinguishable from that in haemolytic disease except for the marked haemosiderosis in the latter condition (Fig. 11). Dilated bile-capillaries, bile-thrombi and small areas of

necrosis or necrobiosis are not uncommonly seen in icterus gravis

The liver in Pepper's type of congenital sympathicoblastoma has a very characteristic appearance. It is enormously enlarged and studded with lentil- to pea-sized [2-4 mm] greyish-white or yellowish nodules, some of which show haemorrhagic areas.

The liver in congenital syphilis is enlarged, firm, reddish-brown or greyish-red, only exceptionally greenish. On section, all traces of lobular structure have disappeared and are replaced by irregular spots and strands of reddish-brown, grey and pinkish-grey tissue. An association of this diffuse syphilitic hepatitis with miliary granulomata is not uncommon, but the latter (erroneously called miliary gummata) are never seen without diffuse hepatitis. The characteristic histological findings need not be discussed here. Smears for Fontana's stain should be always made in addition to Levaditi's stain in sections. Miliary non-syphilitic necroses of the liver are rare, but occur almost exclusively in young infants, the liver being studded with millet-sized [1.5-2 mm] yellowish nodules which are visible both on surface and on section, where they often show a central depression (Fig. 12). Their pathogenesis is obscure, although they are usually associated with severe enteritis or with umbilical sepsis. Similar necroses were described in infantile toxoplasmosis, and were seen by Parsons & Baar (1945) in one of their cases of infective encephalitis resembling toxoplasmosis.

A typical primary tuberculous complex of the liver in congenital transplacental tuberculosis is shown in Fig. 13.

Glycogen-storage disease (van Creveld-Gierke's disease) should be suspected when a very large liver without characteristic naked-eye appearance is found in the absence of a splenic tumour. Apart from investigations for glycogen, the speed of glycogenolysis should be determined. Blood-sugar estimations are of value only if the necropsy is made shortly after death, and only blood from the left side of the heart should be used, never that from the right.

Marked fatty changes in the liver may be found as early as 24 hours after birth.

The ligamentum hepato-duodenale is now inspected, and the portal vein is opened for the presence of thrombosis.

The spleen is enlarged in septic conditions of the newborn, but a typical acute splenic tumour with diffuent pulp is never seen. Large hard splenic tumours are seen in syphilis, in congenital tuberculosis, in biliary cirrhosis, in haemolytic disease of the newborn, in congenital leukaemia and, particularly large, in Niemann-Pick's disease and the infantile form of Gaucher's disease. In sphingomyelin lipoidosis (Niemann-Pick's disease), the liver is also considerably enlarged, and the enormous spleen shows on its cut surface a peculiar salmon-pink colour, sometimes with areas of more greyish-pink colour. Tissue should be taken for paraffin sections, for frozen sections and for lipid analysis (which alone enables a definite diagnosis to be made).

Hodgkin's disease is extremely rare in the neonatal period, but a case of congenital Hodgkin's disease as the result of transplacental transmission has been described by Priesel & Winkelbauer (1926). The spleen is the only organ with an absolutely characteristic naked-eye appearance. It has the features of a "porphyry spleen".

The abdominal aorta and inferior vena cava are dissected and examined. Thrombosis of the abdominal aorta in the

neonatal period associated with anaemic infarction of the liver has been described by Morrison (1945). Thrombi in the inferior vena cava are not rare.

Suprarenal Glands

The pathology of the suprarenal glands is of great importance in the neonatal period. Haemorrhages of the suprarenal are not uncommon as the result of birth-injury, but the writer has never seen the Waterhouse-Friderichsen syndrome resulting from septic infections in the neonatal period. Haemorrhages of the suprarenals should not be confused with the physiological hyperaemia (sometimes erroneously called physiological haemorrhage) of the inner zone of the cortex and its post-mortem softening. Small haemorrhages are often found on histological examination. Even large haemorrhages may be compatible with life, and on two occasions the writer has observed, as an incidental finding in older children, extensive destruction, calcification and deposition of haemosiderin in both adrenals, leaving only about one-fourth to one-third of suprarenal tissue intact. Suprarenal haemorrhage of the newborn is almost invariably associated with intracranial haemorrhages, and is supposed to be the result of asphyxial congestion.

Hyperplasia of the suprarenals is in the newborn female always associated with pseudohermaphroditism. The external genitalia are of the male type, the internal—except for occasional ovotestes (Broster, Clifford, Vines, Patterson, Greenwood, Marrian & Butler, 1938)—normal female. In the rare cases of suprarenal hyperplasia with male gonads there is no pseudohermaphroditism. The prostate is enlarged, the testes are normal. Although in later childhood interrenal pseudohermaphroditism is always associated with precocious growth and ossification, the writer has failed to find any increase in length or premature ossification centres in newborn pseudohermaphrodites with suprarenal hyperplasia. Adrenal hyperplasia in young babies dying with symptoms of gastro-intestinal stenosis has been described by Dijkhuizen & Behr (1940). Two cases of this type were seen at the Children's Hospital, Birmingham, both having been sent to the hospital with the diagnosis of pyloric stenosis.

In normal newborn infants, the suprarenal is about one-third of the kidney's size. In hyperplasia it is not only considerably enlarged but also more firm, and its surface shows numerous deep furrows. Sections of suprarenals should be stained in such cases by the method of Vines (1938), although it is still debatable whether the fuchsinophil granules are the site of androgenic hormone.

Sympathicoblastoma of the suprarenal in the newborn infant has already been briefly discussed. A case of apparently primarily multiple neuroblastomata (=sympathicoblastoma), ganglioneuromata and neurofibromata in a still-born infant has been described by Potter & Parish (1942).

Urinary Organs

The kidneys of the newborn infant show marked foetal lobulation, and in infants more than two days old the so-called "uric acid infarcts" (Virchow) are often seen as golden-yellow radiating streaks in the renal pyramids. The mechanism of their formation is still obscure, but dehydration certainly plays an important role (Czerny & Keller, 1925). In the late neonatal period and in later infancy, dehydration is associated with urate concretions in the renal pelvis, instead of uric acid infarcts. Renal calcinosis, which may be

occasionally seen in the later neonatal period, is in its milder degrees only microscopically recognizable. In more advanced cases dry, white, chalky streaks and spots are seen on naked-eye examination, these are due to lime casts and calcium deposition in necrotic epithelia. They are usually associated with severe diarrhoea and are, in the writer's opinion, secondary to the loss of bases necessitating the use of calcium for neutralization purposes. Severe renal calcinosis may be the cause of uraemia. Extreme hypoplasia of both kidneys is another cause of uraemia in the neonatal period. The size of such a kidney may be that of a bean [12-14 × 4-5 mm]. Focal scarring of kidneys with depressions resembling arteriosclerotic depressions has been seen on one occasion as a result of intra partum haemorrhage. Haemorrhagic infarction of kidneys, total or partial, is not uncommon in the neonatal period, and is the result of thrombosis of renal vein. If the main vein is involved, the thrombus may extend into the inferior vena cava, or a thrombus may be seen projecting out of the renal vein into the latter. Congenital hydronephrosis and hydroureter are only in a minority of cases due to an organic obstruction, and the majority have not yet been satisfactorily explained, although partial gigantism or achalasia of sphincters have been suggested. The latter explanation is more probable, especially in cases with marked hypertrophy of the wall of the urinary bladder. Secondary infection resulting in pyonephrosis may be seen in the neonatal period.

Endothelial proliferation and hyalinization in arterioles and glomeruli (Fig 14), proliferation in the parietal layer of Bowman's capsule and fusion with the tuft are frequently found in kidneys of newborn infants ("congenital glomerulosclerosis") (Herxheimer, 1909, Friedman, Grayzel & Lederer, 1942). They are focal in distribution, usually very scanty, disappear in early childhood, and are probably in the majority of cases without pathological significance (? developmental in origin). It is difficult to correlate these findings with the physiological albuminuria of the newborn, and more likely that the latter is due to the changes in the epithelium of the visceral layer of Bowman's capsule, described by Gruenwald & Popper (1940).

A Wilms' tumour may be congenital. The youngest baby from which a specimen of Wilms' nephroblastoma has been examined by the writer was 6 weeks old.

Haemorrhagic glomerulonephritis has been seen on a few occasions in newborn babies of mothers suffering from eclampsia gravidarum.

Haemorrhagic or gangrenous cystitis is often seen in infants with rectovesical fistula, and is usually associated with unilateral or bilateral pyelonephritis. A urachus cyst interfering with the contractions of the bladder was apparently the cause of urinary stagnation, infection, and pyelonephritis in one case observed at the Children's Hospital, Birmingham.

Gross malformation of the genitalia is occasionally associated with malformation of the urinary tract. Follicular cysts of the ovary are comparatively often found

Intestine

The intestine is dissected with scissors from the rectum upwards to the caecum, the scissors are passed through the ileo-caecal valve, and the small intestine is dissected along its mesenteric insertion. The contents of the intestine are thoroughly inspected. Those of the large intestine give often the only evidence of the presence of an "enteritis". An interesting condition of the early neonatal period is the meconium ileus, which is almost invariably associated with cystic fibrosis of the pancreas. It was first described by Landsteiner (1905). The large intestine is collapsed and almost empty, and a plug of pale inspissated meconium is found blocking the ileo-caecal valve. Similar material, which has been well compared with putty, is found in the small intestine. Occasionally, however, only the lower part of the small intestine contains this material, while green soft meconium may be found in the upper part. These babies die of a diffuse peritonitis.

Blood or blood-stained meconium may be found in the intestine in haemorrhagic disease of the newborn. Ulcers, mainly duodenal, are found only in a few children who have suffered from intestinal bleeding. The haemorrhage is usually parenchymatous and is often associated with submucous haemorrhages. Some authors, however, have reported the frequent finding of tiny ulcers on microscopical examination.

Diarrhoea of the early neonatal period is more often associated with anatomical changes in the intestine than is the case in later infancy. It may be haemorrhagic or ulcerative. "Transmigration" or "permeation" peritonitis is not uncommonly associated with this type of enteritis, and may occur even in an enteritis without gross anatomical changes of the intestinal wall. It is interesting evidence of the immaturity of the neonatal intestine. Haemorrhagic and ulcerative enteritis of the later neonatal period is sometimes associated with intestinal pneumatosis (intestinal emphysema). In this condition, innumerable tiny air-vesicles are seen in the intestinal wall, which on palpation gives a feeling similar to that of an aerated lung. Previously considered as a post-mortem phenomenon, it is now recognized by the majority of authors as an intravital change. On histological examination, the vesicles are usually found in the corium mucosae and in the submucosa. Bacteria are not seen in the surrounding tissue, and in the majority of cases there are no inflammatory changes. The condition is probably due to a mechanical pushing of air through the damaged mucosa by intestinal peristalsis.

In the majority of cases with fatal diarrhoea, in the neonatal period as well as in later infancy, the anatomical and bacteriological findings are negative, except for the frequent fatty degeneration of the liver, and, in spite of the enormous amount of work which has been done to elucidate this most important problem, the pathologist remains puzzled and dissatisfied.

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A SUMMARY OF PRESENT KNOWLEDGE OF HUMAN BLOOD-GROUPS, WITH SPECIAL REFERENCE TO SEROLOGICAL INCOMPATIBILITY AS A CAUSE OF CONGENITAL DISEASE

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Inheritance of the Blood-Groups

Since Landsteiner's discovery of the ABO blood-groups at the beginning of this century a great deal has been learnt about the inheritance of blood-group antigens, but almost nothing about the inheritance of blood-group antibodies. It is still a matter of conjecture why a person who possesses antigen A has anti-B in his serum. The reciprocal arrangement of antigens and antibodies is found as a rule only in the ABO groups, but is not complete in this system, for AB

persons very rarely have anti-O in their serum, and the subgroup antibodies are not regular in their appearance. For example, it is only one in three A₂B persons who has α₁ (anti-A₁) in his serum. This is in such a sharp contrast with the regularity of the appearance of the antigens as to suggest that either the presence of antibodies is not wholly genetically determined, or, if it is, that the mechanism of inheritance is of a more complicated nature than that controlling the antigens.

The antibodies corresponding to the other blood-group antigens seldom occur naturally. For example, a person of group N very rarely has anti-M in his serum. Even more rarely has an M person anti-N. Anti-P is only occasionally found in blood lacking that antigen, and as far as I am aware anti-Rh has not been proved to occur naturally.

It may be said, rather loosely, that all blood-group antigens are dominant mendelian characters—in respect of their equivalent antibody. Several of them are better described by the genetical term "intermediate characters", since the description of a character as a dominant means that two doses of the gene responsible (in the homozygote) have an effect indistinguishable from that resulting from one dose of the gene (in the heterozygote). In the case of the M and N genes there is quite a marked dosage-difference. The erythrocytes of an N (NN) person contain more N substance than do those of an MN person (Landsteiner & Levine, 1928). This effect is also marked in the case of the Rh genes c (Race,

Taylor, Boorman & Dodd, 1943), and C^r (Race, Mourant & Callender, 1946), and e (Mourant, 1945). It is perhaps wiser to avoid the terms dominant and recessive in referring to the blood-group antigens, for these terms are relative to the available antibodies. For example, if only the Rh antibody anti-C was known, then the C antigen would appear to be dominant to c, whereas if only anti-c was known then c would appear dominant to C. (Fisher's notation for the Rh antigens here used is explained below.)

As a general rule it seems that a blood-group gene produces an antigen, and this antigen is capable, under favourable circumstances, of inducing its specific antibody. But there are examples of overlapping in the antigenic powers of the end-product of gene action. The gene A₂, for example, produces the antigen A₂, while the gene A₁ produces the antigen A₁ (Landsteiner & Levine, 1930). Yet the antigen A₁ reacts with two different antibodies α and α_1 , while the antigen A₂ reacts only with the former of these. The Rh gene C^r produces the antigen C^r, and the gene C produces the antigen C, yet the antigen C is capable of inducing the formation of the antibodies anti-C and anti-C^r (Race, Mourant & Callender, unpublished observations). The understanding of such anomalies may have to await greater knowledge of the substances involved. Fundamental biochemical knowledge in this field, as Morgan (1944) pointed out in these columns, is at present very slight.

Immunization

The stimulation of blood-group antibodies in the circulation of a person lacking the equivalent antigen can occur in two ways: (i) A man, or a woman, may become sensitized by the transfusion of blood containing an antigen which they lack, (ii) a woman may become sensitized when pregnant with a foetus which has an antigen, inherited from the father, which she herself does not possess. Several of the immune antibodies to be described have resulted from both processes.

Dienst, in 1905, suggested that a mother might be immunized by the blood of her foetus and that this process might be a cause of toxæmia of pregnancy. Ottenberg was attracted by the same idea, and in 1923 further suggested that jaundice of the newborn might be due to "accidental placental transfusion of incompatible blood."

It was not until 1939 that immunization of a mother by a foetal erythrocyte antigen was proved to occur, when Levine & Stetson described a case of stillbirth complicated by maternal loss of blood. The mother (group O) was transfused with her husband's blood (group O). The transfusion was followed by a severe but not fatal reaction. Later an antibody was found in the mother's serum which agglutinated the cells of her husband and those of 83 out of 104 group O donors. Levine & Stetson concluded that the antigen responsible had been present in the foetus, inherited from the father, and had stimulated the formation of the equivalent antibody in the mother. On receiving the transfusion the mother's antibody had reacted with her husband's cells carrying the antigen. A year later, when Landsteiner & Wiener (1940) had announced their discovery of the Rh groups, the antibody found by Levine & Stetson was identified as anti-Rh. Early in 1941 Levine, Katzin & Burnham demonstrated the causal relationship between the Rh groups and erythroblastosis foetalis.

A single transfusion of blood containing a given antigen may suffice to immunize a recipient lacking that antigen, but

more than one pregnancy is generally necessary before a woman becomes immunized by a foetal antigen, at any rate if the antigen is Rh. The various blood-group antigens will be discussed individually.

The Species Antigens

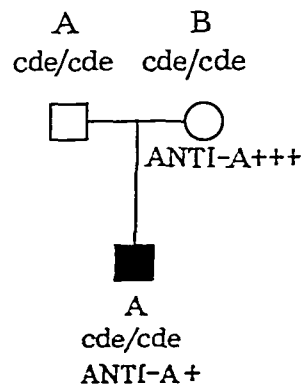
Several reports of 17th century transfusions (Wiener, 1943) describe symptoms due to the incompatible blood which had been given. Human recipients were given blood from lambs or sheep. The urine "black as soot" passed by the recipients was evidence of the effect of species agglutinins on the transfused blood. Had the claim of Mary Tofts, in the early 18th century (Sutton, 1943), that she gave birth to rabbits, not been discredited, one might have looked to her offspring for examples of haemolytic disease of the newborn due to species agglutinins.

The Antigens of the ABO System

The transfusion of blood containing the antigens A or B to patients whose serum contains anti-A or anti-B usually results in a severe reaction, often in a fatal one. Boorman, Dodd & Mollison (1945) have recently reported five such incompatible transfusions.

Iso-immunization to the ABO groups occurs in pregnancy. If a foetus has the antigen A or B, not possessed by the mother, then the titre of maternal anti-A or anti-B is increased. This was first demonstrated by Jonsson (1936) and has been confirmed by Smith (1945). The latter author demonstrated that in such "heterospecific" pregnancies the expected rise in titre of maternal agglutinins does not occur if the child is a non-secretor (that is, if the saliva of the child contains no A or B substance). In spite of this frequent immunization, haemolytic disease due to maternal anti-A or anti-B is almost unknown. The reasons for the protection enjoyed by foetal cells against these antibodies have been studied by Tovey (1945), who considers that several factors are involved, such as lack of placental permeability to anti-A and anti-B, neutralization of these antibodies by A or B substance in foetal plasma, lack of sensitivity of the foetal erythrocytes, and diminished activity of anti-A and anti-B at body-temperature.

FIG 1 HAEMOLYTIC DISEASE DUE TO ANTI A
(from Aubert, Cochrane & Ellis, 1945)



In this and the following pedigrees haemolytic disease of the newborn is indicated by a solid square (male) or circle (female).

Aubert, Cochrane & Ellis (1945) have reported a case of hydrops foetalis, which they attribute to maternal anti-A agglutinin. This is the only convincing example yet published of haemolytic disease caused by the ABO blood groups (Fig 1).

The mother's serum contained a phenomenally large amount of anti-A (titre 1/16 million) and, what is particularly significant, although the baby was group A, it had strong anti-A in its serum (titre 1/128).

The Sub-groups of A

The possibility that a recipient of group A_2 may occasionally make a_1 when transfused with A_1 cells is considered by Wiener (1941). As far as I am aware no conclusive evidence has been produced showing that a_1 has caused either a transfusion reaction or haemolytic disease of the newborn.

The Antigens M and N

The presence of anti-M in the serum of a person of group N has been reported on about a dozen occasions. The majority of these antibodies were considered to be "naturally occurring" rather than immune. Wiener, however, describes anti-M in the serum of a patient of group N, thought to have been produced in response to a transfusion of M blood. As far as I know the only well authenticated case of anti-M causing a transfusion reaction is that of Broman (1944).

Singer (1943) described the first human anti-N agglutinin. It was found in the serum of a patient of group M who had been transfused with N blood (both donor and recipient were Rh positive). A reaction followed subsequent transfusion of N blood, but several pints of M blood were well tolerated.

A strong anti-N has recently been produced by a patient of group M who has shown remarkable powers of making antibodies (Callender & Race, 1946). The anti-N appeared in response to a series of very small (about 0.1 cm³) intravenous injections of N blood. In this case no anti-N was to be found in any of the very numerous samples of serum taken before the immunization. As far as I am aware neither anti-M nor anti-N has been blamed for haemolytic disease.

The Antigen P

Wiener & Unger (1944) reported anti-P agglutinin in the serum of a P negative patient. These authors considered that the antibody was made in response to transfusion. We have in our records five cases of anti-P agglutinin in human beings, but in none was there any good evidence of the antibody being other than "naturally occurring".

The Rh Antigens

Before discussing disease caused by the Rh groups it is necessary to give some key to this complicated system of antigens and antibodies. The Rh groups were last reviewed in these columns two years ago (Taylor & Race, 1944). Since that time several new facts have been disclosed and our understanding of the rather bewildering interaction of antigens and antibodies has been greatly helped by the ideas of Professor R. A. Fisher (Race, 1944; Fisher & Race, 1946). Briefly, Fisher, noticing the mutually antithetical reactions of two of the four types of sera known at the end of 1943 (Race, Taylor, Cappell & McFarlane, 1944), that is to say the 80% and 70% serum (Table I), supposed that these two sera were reacting with allelic antigens. One of these antigens Fisher called C and the other c. The two remaining antibodies did not give antithetical reactions, so the antigens which they recognized were not allelic to each other, though each presumably had an allele. The antigen reacting with the 85% serum was called D and that with the 30% serum E, and their hypothetical alleles were called d and e. Fisher pictured three closely-linked loci, each with two alleles, as responsible for the Rh groups, instead of one locus with seven alleles, as had previously been supposed. As an individual has two of each of the 24 different human chromosomes, he will have two of the Rh chromosomes, either of which may carry any combination of the three alternative pairs. For example, a person may receive CDe from one parent and cde from the other. This combination CDe/cde is the most frequent one in persons of Western European stock. Fisher's theory made several predictions which are gradually being confirmed, most notably by the

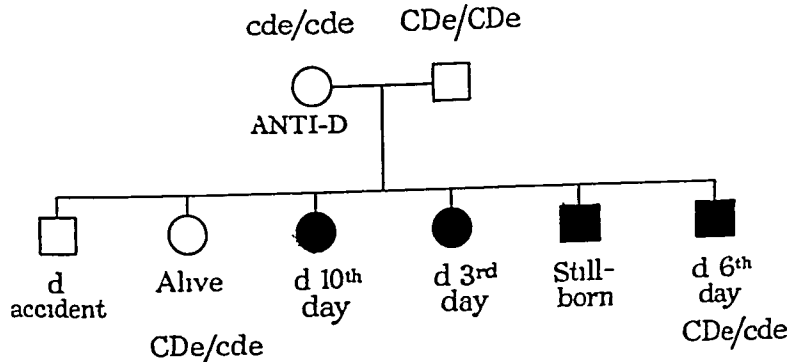
TABLE I RH ANTIGENS AND ANTIBODIES (Race, Mourant & Callender, 1946)

ANTIBODIES		GENES AND ANTIGENS											
European bloods positive		R_0 cDe	r cde	R_0 cDE	R^* cdE	R_1 CDe	R Cde	R_z CDE	R_y CdE	C*De	C*de	C*DE	C*dE
70%	anti-C	—	—	—	—	+	+	+	(+)	—	—	(—)	(—)
85%	anti-D	+	—	+	—	+	—	—	(—)	+	—	(+)	(—)
30%	anti-E	—	—	+	+	—	—	+	(+)	—	—	(+)	(+)
80%	anti-c	+	+	+	+	—	—	—	(—)	—	—	(—)	(—)
(68%)	anti d	(—)	(+)	(—)	(+)	(—)	(+)	(—)	(+)	(—)	(+)	(—)	(+)
98%	anti-e	+	+	—	—	+	+	—	(—)	+	+	(—)	(—)
2%	anti-C*	—	—	—	—	—	—	—	(—)	+	+	(+)	(+)

The left upper compartment shows the interactions known before Fisher's theory was postulated. The middle compartment shows the extension demanded by Fisher's hypothesis, now in part confirmed serologically. The right and lower compartment shows the extensions made, and those suggested by the anti-C* serum. Reactions which have not yet been confirmed serologically are shown in brackets. Anti-C in this table means pure anti-C, and not anti-C + anti-C*, which is the constitution of about half the sera called anti Rh' by Wiener (1944). Wiener's notation for other antibodies is anti-Rh₀ (anti-D), anti-Rh* (anti-E) and anti-Hr (anti-c).

discovery by Mourant (1945) of the predicted anti-e serum. Recently a third allele at the C-c locus, called C*, has been found (Callender, Race & Paykoç, 1945, Race, Mourant & Callender, 1946).

FIG 2. HAEMOLYTIC DISEASE DUE TO ANTI-D HOMOZYGOUS FATHER



The Rh Antigen C

Pure anti-C might be expected as a result of transfusing cDE/cde persons with CDe/cde blood, or when a woman of the former group has a child of the latter. For some unknown reason, however, anti-C has not been found except in the mixtures already mentioned.

The Rh Antigen c

Anti-c was described and its reactions were determined in 1943 by Race, Taylor, Boorman & Dodd. It is rare as a cause of haemolytic disease. Fig 5 shows the pedigree of the St. family investigated by McCall (McCall, Race & Taylor, 1944, McCall & Holdsworth, 1945). Anti-c has been responsible for transfusion reaction (Callender & Race, 1946).

The Rh Antigen C*

A recipient of Rh group CDe/CDe was given blood of group C* De/CDe, suffered a mild reaction and made as a result anti C* (Callender, Race & Paykoç, 1945, Callender & Race, 1946). Anti-C* alone has not yet been proved to have caused haemolytic disease. It has been found in the serum of mothers of haemolytic children, but in the presence of other antibodies such as anti-C and "incomplete" anti-D.

The Rh Antigen D

The antigen D is much the most important, clinically, of the Rh antigens. It is that discovered by Landsteiner & Wiener, and shown by Wiener & Peters (1940) to be a fairly common cause of reaction to transfusion. Levine, Katzin &

Burnham (1941) proved it to be the main cause of haemolytic disease of the newborn.

The presence or absence of D makes a person Rh positive or Rh negative. The importance of D above other Rh antigens depends on its greater efficiency in stimulating the production of antibody, for anti-D is found more frequently than all the other Rh antibodies put together. Since 1940 this antibody must have been proved responsible for haemolytic disease in many thousands of families. Fig 2 and 3 show two pedigrees from our records, the former with a father homozygous in respect of D, and the latter with a father heterozygous in this respect. Mothers with husbands of the Rh groups shown in these two figures sometimes make anti-D only, sometimes anti-D + anti-C, and very occasionally anti-C + the "incomplete" or "blocking" form of anti-D. Frequently the "incomplete" form of anti-D alone is made, and sometimes a mixture of anti-D + "incomplete" anti-D. The first child, or the first two children, are nearly always unaffected in a family with haemolytic disease due to the Rh factor. Levine (1945) has shown that when the first child is affected the mother usually has a history of past blood transfusion.

FIG 3. HAEMOLYTIC DISEASE DUE TO ANTI D HETEROZYGOUS FATHER

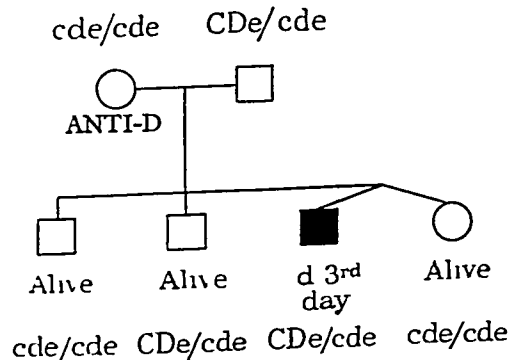
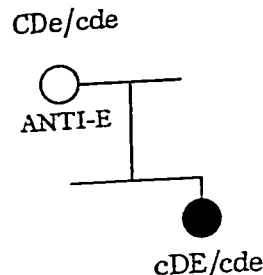


FIG 4. HAEMOLYTIC DISEASE DUE TO ANTI E



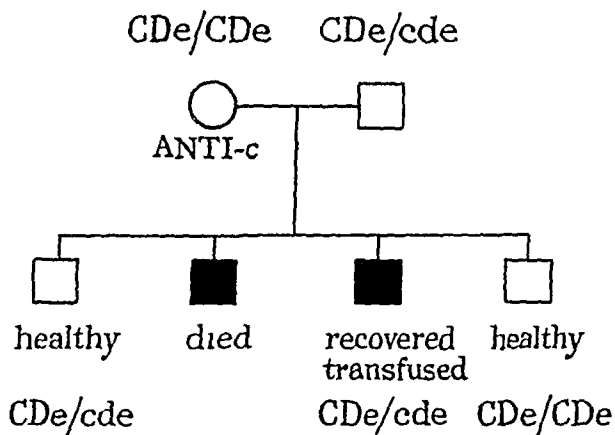
The Rh Antigen E

We have several examples of transfusion reactions due to this antibody. Fig 4 shows a family in which pure anti E caused haemolytic disease. In appropriate matings anti-E is sometimes found together with anti-D.

The Rh Antigen e

Until the discovery by Mourant (1945) of the anti-e serum the antigen e was in the position still occupied by d, the presence of which in a blood is detectable only as an absence of D. Mourant found the anti-e in the serum of a patient cDE/cDE who had been given many transfusions with increasingly severe reactions. Transfusion with cDE/cDE blood was completely successful.

FIG. 5 HAEMOLYTIC DISEASE DUE TO ANTI-c
(from McCall, Race & Taylor, 1944, McCall & Holdsworth, 1945)



The Lutheran Antigen

This antigen, present in about 1 in 12 of the English population (Callender, Race & Paykoç, 1945, Callender & Race, 1946), has caused the formation of the corresponding antibody, anti-Lutheran, in a recipient of blood transfusion. It is not known whether it has the power to cause a reaction, for Lutheran-negative blood was used for subsequent transfusions of this patient. The Lutheran antigen is apparently not connected with any of the known blood-groups.

The Kell Antigen

Another antigen, "Kell", which also seems not to be connected with any of the known blood-groups, has probably been responsible for haemolytic disease of the newborn in the family shown in Fig 6 (Coombs, Mourant & Race, 1946). The mother, who was "Kell"-negative, had in her serum an antibody which agglutinated the cells of her children, her husband, and about 7% of random bloods. The baby's cells were shown by the rabbit anti-human-serum serum test (Coombs, Mourant & Race, 1945) to have been sensitized *in utero*. The baby was severely anaemic, but not jaundiced, and responded well to a blood transfusion.

Miscarriages

The important paper of Levine (1943) on "Serological factors as possible causes in spontaneous abortions" has drawn attention to, and supports, the possibility first pointed out by Hirsfeld, that there may be a differential survival-rate depending on the ABO blood-groups of mother and foetus. It was found that more A children resulted from A x O matings, when the mother was A, than when the mother was O. [102 families of these two types of mating, grouped at the Galton Laboratory, failed to show this difference however (Taylor & Prior, 1938, Race, Ikin, Taylor & Prior, 1942). Further, a series of 112 bloods sent

to this laboratory from mothers who had had early miscarriages shows no obvious disturbance of ABO group frequency (Woodward & Race, 1946)].

Anti-Rh and the ABO Groups

In the same paper Levine notes for the first time the curious fact, which still lacks adequate explanation, that matings which result in the production of maternal anti Rh are far more often compatible, or homospecific, on the ABO system than are normal matings. This has been the persisting experience of the Galton Laboratory and of Professor Cappell's and Dr Plaut's departments. There is no possible doubt about the statistical significance of these findings.

Toxaemia of Pregnancy

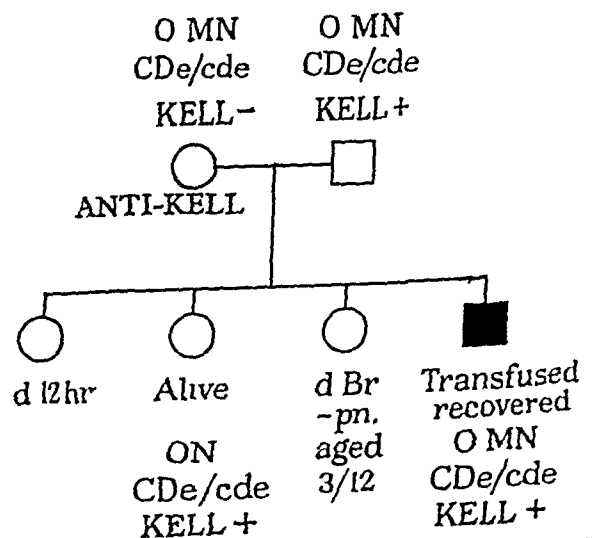
The question raised by Dienst, over 40 years ago, as to whether blood-group incompatibility between mother and foetus is a cause of toxaemia of pregnancy, still seems to remain without definite answer. Dr Marjory McFarlane has kindly allowed me to quote the following unpublished figures. Of 59 Dundee women suffering from severe toxaemia of pregnancy, 34 were group O, 15 group A, 7 group B, and 3 group AB. This does not differ significantly from the normal Scottish distribution, and the same can be said of the Rh groups, there being 47 Rh positive and 12 Rh negative.

Rh and Mental Deficiency

Two groups of workers in the United States, Yannet & Lieberman (1944) and Snyder, Schonfeld & Offerman (1945), found an apparently significant distribution of Rh groups in "undifferentiated" mental defectives and their mothers, too many of the mothers being Rh negative¹. On statistical grounds, Professor Penrose (personal communication) has thrown doubt on the significance of these findings, and work is now in progress which, so far, supports Penrose's views.

The blood-group genes are not known to exert other effects on the carrier, though there are theoretical reasons for thinking that this may occur. The blood-groups have so far

FIG. 6 THE KELL FAMILY
(from Coombs, Mourant & Race, 1946)



¹ See the leading article in the *British Medical Journal* 1945 2, 183

been shown to be capable of causing two disease states reaction to transfusion can be due to the ABO or the Rh

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groups, and haemolytic disease of the newborn is almost invariably due to the Rh groups

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MATERNAL RUBELLA AS A CAUSE OF CONGENITAL DEFECTS

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In the first six months of the year 1941, Gregg (1941), an ophthalmic surgeon of Sydney, Australia, saw an unusual number of infants with congenital cataract almost amounting to "a mild epidemic". The majority of the mothers of these children gave a history of an attack of rubella during pregnancy, and he found that the early periods of their pregnancies "corresponded with the maximum intensity of the very widespread and severe epidemic in 1940 of the so-called German measles". Furthermore, in his opinion, the

cataracts did not "exactly correspond to any of the large number of morphological types of congenital and developmental lenticular opacities that have been described"

Actually 13 infants having congenital cataracts came under his own care and 7 others under that of his colleagues, moreover, he knew that similar cases had occurred during the same period in widely separated parts of Australia. He therefore communicated with colleagues in New South Wales, Victoria and Queensland and altogether was able to collect 78 cases. The cataract was usually bilateral, but in 16 instances it was monocular, in 10 of these infants it was associated with microphthalmos, and in a few cases there was also a corneal haze.

Frequently the babies were small in size, ill-nourished and difficult to feed, and 44 of them also suffered from congenital heart disease. In 68 instances the mother gave a history of rubella during pregnancy, and in the majority the illness occurred in the first or second month of pregnancy. A majority of the mothers contracted the disease in July or August 1940, and in the remainder the time of incidence of the disease was spread over the period December 1939 to January 1941. Returns from hospitals in Sydney showed that the peak of the epidemic occurred from the middle of June to the early part of August 1940. In 26 instances, out of a total of 35 mothers in which the record was available, the affected children were first children, and it was the young

adult group to which these primiparae belonged which was particularly affected by the epidemic Gregg thought that this 1940 epidemic of German measles "differed greatly from the ordinary virus infections bearing that name". He said that he had never seen such severe examples of the disease or such severe complications, adenopathy, sore throats, involvement of ankle and wrist joints and the general constitutional symptoms were all very pronounced, and the rash was pleomorphic, being "macular, morbilliform, scarlatiniform and toxic erythematous". Co-incidentally with this epidemic there also occurred in military camps epidemics of sore throats, which spread to the civilian population.

All these points made Gregg wonder whether the illness was or was not rubella, but he came to the conclusion that it really was that disease and even speculated as to the possibility that the few mothers of infants with congenital defects who failed to give a history of rubella in pregnancy had suffered from mild attacks which had been overlooked. Although there is no definite statement to the effect that congenital defects are particularly prone to occur in severe epidemics of German measles, such a condition of affairs is certainly implied in this and other papers on the subject, it would, therefore, seem somewhat illogical to claim that attacks of rubella so mild as to pass unrecognized were also responsible for such defects.

South Australian Survey

Impressed by Gregg's findings and knowing that similar cases had occurred in South Australia, Swan of Adelaide and his colleagues conducted a survey which was supported by the National Health and Research Council of Australia. They have reported their results in a series of papers (Swan, Tostevin, Moore, Mayo & Black, 1943, 1944, Swan, 1944). For the purpose of this survey, they issued a questionnaire to general practitioners in South Australia and also asked for permission, if the mother lived in Adelaide, to question her about her past medical history and, if a pregnant woman was known to have rubella, to be allowed to see her and to follow her progress through pregnancy until the birth of her child.

The cases investigated occurred in the years 1939 to 1943, but it was not until 1942 that the "follow up" method was used, previously the enquiry had been a retrospective one. In all they collected information concerning, or examined, 74 mothers, the diseases from which they suffered during pregnancy and the numbers of their offspring who had congenital defects are shown in the following table.

Mothers	Disease	Infants with defects
57	Rubella	40
1	Rubella and measles	1
2	Rubella and mumps	0
1	(?) Rubella and (?) measles	0
7	Measles	0
1	Mumps	1
1	'Influenza'	1
4	None	4
74		47

The defects found were defects of the eye and heart, deaf-mutism, mental retardation, etc., moreover, there was often more than one defect in the same child, and many of the children were under-developed and difficult to feed.

Evans (1944), working on the same material, described dental defects.

As a result of their survey, these investigators came to the conclusion that "when a woman contracts rubella within the first two months of pregnancy it would appear that the chances of her giving birth to a congenitally defective child are in the region of 100%, and if she contracts it in the third month about 50%".

Welch (1945) has collected the numbers of congenitally deaf children born in New South Wales for each year from 1931 to 1941, in only one year, 1938, did they reach double figures, when they were 47, the mothers of 34 of whom developed rubella during the first four months of pregnancy. An interesting point in this connection is that this large number occurred two years before the severe epidemic of rubella in Australia, referred to above.

Observations in Britain and U.S.A

Subsequently to the original Australian observations, the association between rubella in the mother and congenital defects in the child was also noted in America and England. The number of instances reported from America is not large, the largest series being reported by Erickson (11) (1944) and Albaugh (9) (1945). In England many paediatricians have seen isolated examples of the association, but by far the largest number of cases so far reported is that by Martin (1946), who, by means of a questionnaire, attempted to find the cause of deafness in deaf children who were born in the years 1940 and 1941, i.e. children born after the 1940 epidemic of rubella which was widespread and rather more severe than usual. Altogether she obtained particulars of 102 children, in 15 of whom the deafness was hereditary and in 8 followed meningitis, but 36 of the mothers, 20 of whom were interviewed, contracted rubella during the first four months of pregnancy and 6 others probably suffered from the disease.

Multiple Defects

In a number of these children there was also a defect of the eyes, and in a few, of the eyes and heart. Weston Hurst (Swan *et al.*, 1943) explains the not infrequent association in the same child of congenital heart disease and congenital cataract by assuming that the action of the virus is primarily on vascular structure and that cataract, for instance, follows interference with nutrition of lens fibres brought about by action of the aetiological agent on the hyaloid artery. In a histological examination of material from three fatal cases, Swan (1944) found evidence of an even more widespread attack on the tissues of the embryo, and pointed out that the restriction to the glomeruli of the lesions which he found in the kidneys supported Hurst's theory.

Some Difficulties of the Theory

The statistics given above constitute a strong *prima facie* case for the thesis that rubella in the early stages of pregnancy is likely to cause malformations in the foetus. Certain criticisms, however, must be answered satisfactorily, and further statistical studies are necessary, before the thesis can be regarded as proved. Obviously, the first question requiring an answer is whether the disease from which these expectant mothers suffered was in fact rubella. Although claims have been put forward that rubella has been transmitted to animals, these have not been generally accepted and there is, therefore, no specific serological test available. It has

been suggested that the presence of Türk cells in the blood can be regarded as a diagnostic feature in rubella, but this is an uncertain and unreliable sign, since these cells are also found in other conditions. The diagnosis, therefore, has to be made on clinical grounds, by the exclusion of other diseases which resemble rubella, and by any specific tests available for these exanthemata.

Swan and his colleagues state that exanthema subitum, erythema infectiosum, measles, scarlet fever and glandular fever might be confused with rubella, but that, except in a few cases, a detailed analysis of the symptoms of the mothers in their series failed to support any other diagnosis than that of rubella. Of the exanthemata mentioned by Swan *et al*, scarlet fever and glandular fever are the most difficult to differentiate from rubella. As pointed out previously, epidemics of sore throats occurred in military camps in New South Wales in 1940, and these spread to the civilian population. Gregg (1941) thought that these were streptococcal in origin. Similar epidemics also occurred in South Australia ("Woodburn sore throat") in which the causal organism was *H influenzae*, but in 1943, when Swan and his colleagues wrote their first paper, this epidemic had ceased, although congenital deformities associated with maternal rubella were still occurring.

Another difficulty in diagnosis is the fact that in rubella the rash is often so fleeting and the symptoms are so trivial that little notice is taken of the condition and a doctor is not consulted. The Australian observers, however, stressed the severe character of the 1940 epidemic, and the epidemic in Britain in that year showed more severe symptoms than is usual in epidemics of this disease. According to Weston Hurst (personal communication), the reason for the severity of the disease in Australia, and for the occurrence of so many cases in young married women, was the long freedom of the Australian population from epidemic rubella with the result that a large number of primiparae were at risk. In his opinion, it was the exposure of this large number of non-immune pregnant women to the infection which made recognition of congenital defects in their babies inevitable, and he is convinced of the association between the two conditions, moreover, he quotes as evidence of the severity of the disease the fact that half his staff at the Institute of Medical and Veterinary Science, Adelaide, which was predominantly a young one, were away with the disease at one time.

The change in the type of rubella may have been due to the development of a new capacity by the virus, or the epidemic might even be a new virus disease, but it is much more likely that the change was determined by the unusual opportunity presented by the presence of a large adult population susceptible to the infection.

A second question is why a disease which is so often so mild in the adult should produce such disastrous effects in the foetus? The answer given is that in mammals embryonic tissue is more susceptible to infection than adult tissue, moreover, this susceptibility is most marked in the early stages of development, and it is with the occurrence of rubella early in pregnancy that deformities have been found to be associated. A weak point in this argument, however, is the fact that the Australian workers found that other virus diseases—measles in particular—did not produce these deformities, although there is always the possibility that the effect of the more severe virus infection was to produce abortion.

Two other criticisms of the Australian investigations have been made, first, that in most of the recorded cases the enquiry as to the occurrence of rubella during pregnancy was retrospective, having been made when a congenital deformity was found in the newborn child, and that there are only scanty data concerning mothers who had rubella during pregnancy but gave birth to normal children. Swan and his colleagues did, however, examine a few cases non-retrospectively (positively, to use their phrase), and also found that 17 expectant mothers who developed rubella gave birth to normal children.

Secondly, the effect of other virus diseases on the expectant mother has not been adequately investigated, although in the Adelaide series the children of 7 mothers who suffered from measles during pregnancy were normal.

The available evidence supports the view that the Australian epidemic was due to rubella and, apart from the number of cases they collected, the most important and suggestive facts observed by the Australian investigators were, first, the important epochs in the development of the organs in which abnormalities were found—eyes, heart, teeth—are in the early period of pregnancy, just at the time during which it is stated that their mothers contracted rubella, secondly, congenital abnormalities were not found in the offspring of those mothers who had measles in early pregnancy.

There are no statistics available to show whether or not in the years following the 1940 rubella epidemic in England and Wales there was any increase in congenital malformations which are compatible with life. As far as deaths from malformations are concerned, there was no increase in children under 4 weeks nor from 4 weeks to 12 months in the year 1941, i.e. the year following the epidemic.

Statistical investigations to confirm or refute the association between maternal rubella and congenital deformities are difficult to carry out adequately because large epidemics are infrequent and the section of the population at risk on which they have to be carried out is a small one, indeed, it has been estimated that to obtain a really good statistical result, it would probably be necessary to include in the survey all the married women in England and Wales. A recent investigation in Milwaukee, Michigan, by Fox & Borten (1946), illustrates the difficulty in obtaining a sufficient number of cases and is also interesting in that, although the number of children investigated was small, the results obtained did not support the Australian thesis. In the city of Milwaukee, which has over half a million inhabitants, there is an epidemic of rubella about every ten years, and in the last twenty years there have been 44,482 cases of the disease. The investigators paid particular attention to the 1942-43-44 epidemic, with the following results:

	1942	1943	1944
Total number of cases	3 998	17 703	525
Total number in married women	73	477	31
Total number of married women investigated	19	122	10
Number of babies born to these women	1	9	1

Five of the mothers of the babies had rubella in the first 2 months, four in the 2nd 4th month, and one each in the 7th-9th month of pregnancy. Although one mother who had rubella at the end of the 1st month of pregnancy was delivered of a hydrocephalic still-born baby, there was not a single example of congenital deformity amongst the eleven babies,

and an interesting thing is that one mother who contracted rubella in the 2nd month of pregnancy produced a normal baby, whereas in a previous pregnancy her baby had bilateral cataract

Conclusions

Rubella is not a notifiable disease in England and Wales, although it has been notifiable in the City of Manchester for some years, and it probably would be a help in the solution of the problem under discussion if it were, at any rate, in married women, made universally notifiable. Second attacks of rubella are rare, and therefore the Australian investigators suggested that pooled or adult serum might be used to confer passive immunity upon the expectant mother who had been exposed to the disease. The use of gamma globulin has also been suggested, but even more potent would be the gamma

globulin fraction of rubella convalescent serum. The period of passive immunity is, however, short, perhaps not more than 2-3 weeks, and the injections would have to be repeated either until the woman had reached the 5th month of pregnancy or until there was no longer any risk of infection, whichever were the shorter period.

None of these preparations is available in Great Britain, and it therefore follows that the expectant mother should be guarded from exposure to the risk of infection with rubella, and perhaps of infection with other exanthemata also. There is, of course, one obvious practical drawback to any method of prevention or treatment, namely, that the ill-effects of rubella are produced, if at all, in the early weeks of pregnancy, and the mother may well be exposed to or even develop the disease before she realizes that she is pregnant.

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NOTE—In a letter received by the author since this paper was written, Gregg states that he has seen or collected an additional 138 cases, 130 of which were in the year 1944, making a total of 206 examples of this association between maternal rubella and congenital defects. In the group of 130, the distribution of the defects was as follows

Cases	Deaf-mutism	Congenital heart disease	Eye defects
85	present	—	—
17	present	present	—
5	—	present	—
6	—	—	present
8	—	present	present
8	present	present	present
1	present	—	present

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SOME APPLICATIONS OF PRENATAL NUTRITION TO INFANT DEVELOPMENT¹

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The development of the infant depends upon the development before birth, the one is continuous with the other. A child that is healthy at birth is likely to continue in health in its

postnatal life. There are two main prenatal factors, the genetic and the nutritional, which will impair the chances of survival or improve the health of the infant. This paper deals with the nutritional. A cardinal difference is that these latter can be controlled, but the former, once the ovum is fertilized, are at present beyond our control.

Biological experiments on this subject have been mostly performed upon animals and confirmation upon the human subject is limited, largely by reason of the general difficulty associated with human experimentation, which is intensified in this case by the interesting condition of the subject.

Birth-weight

The infant at birth in health has lived and grown in utero on food supplies which have reached it from the mother across the placenta. Its curve of growth is not normal but is steep in the last three months of intrauterine life, more than two-thirds of the birth-weight being deposited in the last eight weeks. Three-quarters of this birth-weight is

¹ Lecture delivered at the Institute of Child Health, Great Ormond Street London, 10 May 1946

TABLE I COMPOSITION OF THE HUMAN FOETUS IN GRAMS

	Body	Water	Protein	Fat	Ash
End of 5th lunar month	300	260	22	3.5	1.5
End of 7th lunar month	1 000	800	100	25.0	30
End of 10th lunar month (birth)	3 200	2 420	400	350.0	90
Average of daily deposition					
1. Throughout foetal life	11.4	8.6	1.4	1.25	0.32
2. In last 3 lunar months	26.2	19.3	3.57	3.87	0.71
3. In last month	35.7	23.6	6.4	6.4	2.0

water. The daily rate of deposition is shown in Table I, where it is seen to rise steeply in the last part of pregnancy, the average daily increase being 11.4 grams a day throughout pregnancy and 35.7 grams in the last month.

Pronounced depletion of the maternal food supplies lowers the birth-weight (rats Zuntz, 1919, guinea-pigs Paton, 1903, rabbits Reeb, 1905, sheep Hammond, 1932). Moderate underfeeding, however, does not decrease the birth-weight (sheep Hammond, 1932, cow Eckles, 1919, gilt¹ Hogan, 1928).

The best and most recent work is that of Wallace (1944, 1946). He fed pregnant sheep on diets which maintained weight, restricted (low-plane) diets, and high-plane diets of concentrate and excess rations. His results are summarized in Tables II and III.

Wallace demonstrated that the diet in the last eight weeks of pregnancy was important in that it not only raised or depressed foetal growth, but a high-plane diet also caused mammary-gland growth yielding a high milk-yield, of which the more vigorous lamb took full advantage. Still more important was his demonstration that the restricted rations not only depleted tissue-growth but also retarded physiological development, as shown by absence of temperature control and high mortality in neonatal life. The effects of restricted diets were more pronounced with twin births.

In the occupied European countries there has also been observed a corresponding decrease in birth-weights and increase in neonatal mortality. There was, however, a decrease in pregnancy toxæmia, which accords with Wallace's observation that low-plane diets produce increase of liver fat. In Britain, the moderate restrictions of diet due to the war did not lower the birth-weight (Huggett, 1944).

Hammond (1932) has also shown that, with a low plane of nutrition, such that the ewe is ill-nourished at birth, the weight of individuals in twin or triplet lambs is definitely impaired. The result is that ratio

$$\frac{\text{weight of single lambs}}{\text{weight of individual twin lambs}}$$

is proportional to the degree of nutritive impairment. He inferred that in general the chance of survival was inversely proportional to the value of this ratio. Applying this ratio to the birth-weights in London in 1938-1939, and in 1941 and 1942, there is actually an indication of improved health and chance of survival.

The birth-weight is dependent not only upon breed (Eckles, 1919) and food supply of the mother, but also upon the demands of competing metabolisms for the food supply. The main competitors are other animals in the litter, e.g. twins, triplets or multiple litters, the metabolism of the mother

if still growing, and finally the placenta itself. In sheep, individual members of twins are 23% and of triplets are 30% lighter than singletons (Hammond, 1932). In general, the size of individual young at birth is inversely proportional to the number in a litter in the pig, guinea-pig, rabbit and rat.

Curiously enough, the ratio is smaller for male than for female lambs. Hammond regards this as suggesting that males stand a better chance of survival than females. There is no known explanation for this based upon the actions of the sex hormones.

TABLE II INFLUENCE OF HIGH-PLANE AND LOW-PLANE DIETS IN LAST 8 WEEKS OF PREGNANCY ON BIRTH-WEIGHT AND POSTNATAL GROWTH (Wallace, 1944, 1946)

Diet	High-plane	Low plane
Effect on ewe weight pounds	44 (gain)	11 (loss)
Birth weight pounds	10.4	6.8
Milk yield in 3rd week pounds	50	30
Milk yield over 16 weeks pounds	443	292
Lamb weight at 16th week pounds	72	56
Temperature-control at birth	Present	Absent
Neonatal mortality	Nil	High

TABLE III COMPARISON OF EFFECTS OF HIGH PLANE (H.P.) AND LOW PLANE (L.P.) DIETS IN EARLY AND LATE PREGNANCY UPON THE FOETAL GROWTH AND UDDER DEVELOPMENT (Wallace, 1944, 1946)

	Group 1		Group 2	
Diet of ewe in 1st 4 weeks	Maintenance		Maintenance	
Diet of ewe in next 9 weeks	H.P.		L.P.	
Diet of ewe in next 8 weeks	$\frac{1}{2}$ H.P.	$\frac{1}{2}$ L.P.	$\frac{1}{2}$ H.P.	$\frac{1}{2}$ L.P.
Average foetal weight (pounds)—				
At 56th day	17	17	17	17
At 144th day	113	65	111	58
Udders—glandular growth	—	—	—	—
Fat in liver	—	—	—	—

¹ A young sow

The competing effect of the maternal metabolism is shown by the influence of the weight of the ewe at birth on the weight of her lambs—as she gets older their average birth-weight rises. In Suffolk sheep, with young ewes the average twin weight is 11 pounds [5 kg], and with adult ewes the average twin weight is 12 pounds [5.5 kg.] (Hammond, 1932). The same effect is seen in India, where the birth-weights from child-marriages are smaller than those from adults, and rise with increasing age of the mother.

The weight at birth influences the growth after birth (Marshak, 1936, Greene, 1931). Illingworth (1939) has drawn attention to the effect of low birth-weight in humans, and has shown that under modern conditions of civilization it may result in failure to attain normal weights. The work of Wallace (1944, 1946) shows a reason for this imperfect growth after a low birth-weight. The foetus on the restricted diet is equivalent to a premature animal without temperature control and poor in vigour and strength, which feeds at a poorly-developed breast yielding a poor supply of milk. Hess & Chamberlain (1927) have shown, however, that underweight infants can, with special care in feeding, attain normal weights in four years. This special care, however, involves prolonged dietary supplementation, organization and expense.

TABLE IV. BIRTH-WEIGHTS (POUNDS) IN LONDON IN 1938-1939, 1941, & 1942

Year	Mean birth weight in singletons	Individual birth weights of twins	Ratio of singleton weight to individual twin weight
1938-39	7.260	5.237	1.388
1941	7.125	5.125	1.390
1942	7.216	5.448	1.325

This raises the important question of whether the child who has been imperfectly nourished in prenatal life and has enjoyed a high plane of nutrition after birth can ever entirely recover vigour and health. It has been shown in the post-natal sheep (Hammond, 1932) and in the pig (McMeekan, 1940) that, after birth, different organs and portions of the body have different ages of optimal growth. Bone grows first, then muscle and then fat. Bone-length is an earlier growth than bone-breadth. If, therefore, the lambs start, say, on a low plane of nutrition, and are later put on to a high plane, their recuperative powers are limited mainly to those tissues growing mostly in the later period. The bodily proportions are therefore different to those of animals continuously on a high plane of nutrition. It was found, further, that there is some permanence of these effects of nutrition on body proportions (McMeekan & Hammond, 1940).

Wallace (1945) has shown a similar result during foetal life. Low-plane foetuses contrasted with the foetuses of mothers on a high-plane diet, had a differential impairment of tissue- and organ-growth, the nervous system being least affected, bone more so, muscle and flesh most. The alimentary canal was less affected than the heart, lungs, and kidneys, and the thymus, spleen, and liver were most depleted by low rations in pregnancy.

The Theory of Partition of Nutrients

It is desirable to know how the foetus is relatively successful in maintaining its body-weight, and the individual tissues apparently maintain themselves against under-nourishment, when the maternal food is in short supply.

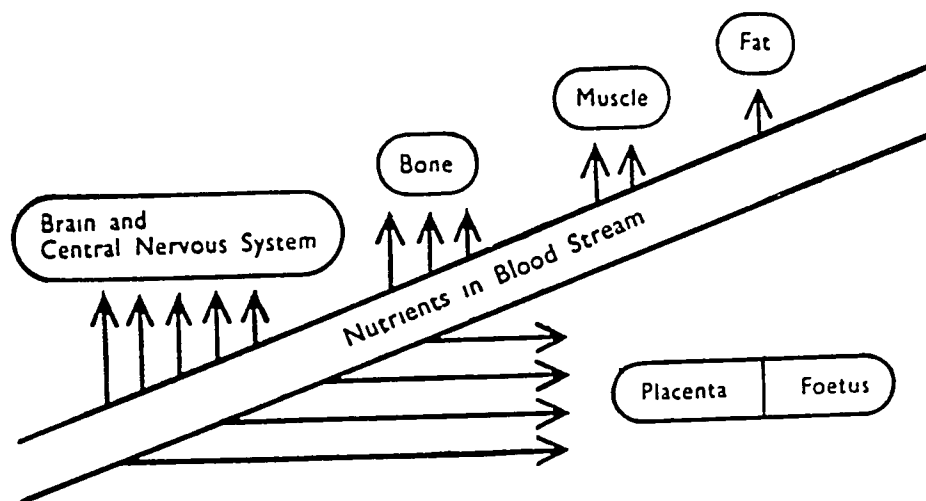
Hammond (1944) has proposed the theory of partition of nutrients, which states that the tissues having the highest metabolic rates have a priority of supply of all nutrients over those tissues and parts with a lower metabolic rate. This view was first developed by Child (1920), who first held that in different tissues of an organism there is an axial pattern of function which involves, amongst other things, a gradient of oxygen consumption correlated chemically with external factors. This means that there is a division of foodstuffs in proportion to the metabolic rate of the tissues concerned, those with the highest rates having the highest priority. Child's thesis that the metabolic rate governs the supply of nutrients has been adopted by Hammond as the basis of his theory, and is supported by the demonstration that there is a correlation between the rates of growth in young animals and their chemical composition (McMeekan, 1940). To give one instance, after birth the first tissue to grow is the bone, followed by the muscle and the depot-fat. In the early stages the first lipids found are in muscles, and are intracellular lipids of high iodine value with great chemical activity, the "élément constant" of Terroine (1920). Later, after the optimum growth of muscle has passed, the lipids deposited are those which form the depot-fat. These are relatively inactive and with low iodine value, the "élément variable" (Callow, 1935). At this stage, the growth-rate for bone and muscle is low and the animal is fattening. A similar parallelism has not so far been demonstrated for the prenatal fat, but it is known that the metabolic rate in foetal tissues is higher in the embryo than in the adult.

Taking these facts into account, therefore, Hammond (1944) has suggested that in early life the high total metabolic rate of foetal tissues enables the foetus to compete successfully with the relatively low metabolic rate of the maternal tissues, and so to obtain its desired nutriment.

He illustrates this by Fig. 1, in which the number of arrows denotes the metabolic rate and tissue's growth. As the supply of nutrients is decreased, the number of arrows is reduced, first fat losing its one arrow, muscle being reduced to one, bone cells to two and brain to three and the placenta plus foetus to three arrows. With further reduction in food supplies the fat and muscle arrows may even be reversed, while bone and brain grow at still further reduced rates. At this stage the maternal tissues waste and lose weight. With ageing of the embryo, its metabolic rate falls and the foetus competes with less priority and with greater difficulty with the maternal tissues.

This hypothesis Hammond supports (1944) by several instances. The instance of the twin lambs at birth being individually 23% lighter than singletons is duplicated in humans. For example, in a comparable series in London, singletons at birth weighed 7.26 pounds [3.29 kg.] and twins 5.24 pounds [2.39 kg.] (Huggett, 1944). When the lambs were fed at the breast, the ratio of singleton- to twin-weights increased (signifying greater relative food shortage), but when the lambs were later weaned and fed on grass the ratio became smaller.

FIG 1 PRIORITY OF PARTITION OF NUTRIENTS ACCORDING TO METABOLIC RATE (Hammond, 1944)



The number of arrows indicates the relative metabolic rate of the different tissues and its satisfaction by a flow of nutrients from the maternal blood stream

This is still more evident with litters. In rabbits, litters of 8-11 had individuals averaging 45 g birth-weight, but with only 1-2 young they averaged 95 g. (Wishart & Hammond, 1933) But if unlimited food was given to the mother it was not possible to increase the birth-weights of the large litters, and this suggests some type of maternal control.

The placenta is a competitor. In the human at full term it bears a ratio to the foetus of one quarter to one twelfth. Clearly, the larger the placenta the better the storage capacity in the middle trimester and the diffusion capacity in the final trimester, and so the greater chance of foetal survival. If we compare the ratio of placental weight to foetal weight (P/F), we find that it becomes smaller as the placenta loses weight and the foetus grows (Huggett, 1941b).

TABLE V THE RATIO OF PLACENTAL TO FOETAL WEIGHT (P/F), AT DIFFERENT AGES FOR SINGLETON AND SIB FOETUSES (SHEEP)

Age in weeks	10	12	14	16	18	20	22
P/F single embryos	1.7	1.3	0.98	0.69	0.43	0.27	0.20
P/F sib embryos	2.3	2.3	0.10	0.78	0.50	0.31	0.22

Similarly at the 21st day of pregnancy in the rabbit, the average P/F ratio is 0.83 for litters of 8-14 embryos, but 0.71 for litters of 7 or fewer embryos (Huggett, 1929).

It seems therefore that the placenta can compete successfully with the embryos in mid-uterine life (before it shows the normal signs of physiological degeneration characteristic of late-uterine life), and the greater the competition for nutrient the more the disparity between the placental and foetal weights. Nutrient supply, however, is not the only factor controlling weight, since when individual cases are considered they show overlap in the ratios. We have, however, another case of Hammond's theory of partition of nutrients.

We can now consider other conditions which have been

known for some time but which are all covered by the generalization of Hammond—namely, the effects of shortage of individual foodstuffs. Hammond applies his theory not only to the gross aggregate total of nutrients but also to any one individual nutrient. Of these one of the most striking is that supply of nutrients concerned with the development of the erythrocyte and provision of adequate haemoglobin.

The Development of the Erythrocyte

In 1931 a considerable body of work emerged which has altered our ideas concerning anaemia in infancy. Mackay & Goodfellow (1931) focused attention on anaemia in infancy by showing that 45% of breast-fed and 51% of artificially-fed infants in an orphanage—working-class population of London—showed anaemia at 12 months of age. This anaemia was accompanied by a big rise in morbidity. It was entirely relieved by the administration of iron, with an accompanying decrease in morbidity and increase in weight. The anaemia was associated with anaemia of the mother in 50% of cases, it was also a progressive condition in the first year of life, which, however, could be reversed by iron medication. It was aggravated or precipitated by any type of jaundice in the infant, by oedema, or by replacement of human by cows' milk, and was associated with birth-weight, in that small infants at birth grew relatively more rapidly than big infants and seemed to develop anaemia more easily.

Mackay & Goodfellow attempted to give extra iron to the pregnant mother with a view to assessing its effect upon the incidence of anaemia in the infant after birth, but the experiment broke down due to conditions beyond their control. However, the experiment was attempted with success by Strauss in 1933 under easier conditions. He investigated pregnant women in whom the maternal anaemia was very low, an average of 36% haemoglobin compared with 76% in the control cases. In both groups there was no significant difference at birth, but at 12 months the infants of the anaemic mothers had only 46% haemoglobin (controls

showing 67%) together with microcytosis and poikilocytosis. He demonstrated that administration of iron in good dosage to the mother during the last three months of her pregnancy not only relieved her anaemia but also gave a normal blood-picture in her infant 12 months after its birth. The infants of the treated mothers had 70% of haemoglobin compared with 46% in the infants of untreated mothers. Both groups had exactly the same average haemoglobin at birth. Iron medication of the mother had therefore had no elevating effect on the circulating foetal haemoglobin.

These observations of Mackay and of Strauss were confirmed by Smallwood (1936) in a parallel experiment in rats and humans. He showed that an iron-deficient diet for pregnant rats produced young with a normal haemoglobin percentage, but with a microcytosis at birth which rapidly developed into a hypochromic anaemia. In his parallel observations, the administration of iron to normal women in pregnancy, while causing no apparent change in the mother or her offspring at birth, did, however, markedly decrease the postnatal drop in haemoglobin. His colleagues Parsons, Hickmans & Finch (1937) carried this further and showed that, if the rats were kept for several generations on an iron-deficient diet, there was a greater anaemia, subnormal weight, and difficulty in rearing and reproducing when the young grew to adult size.

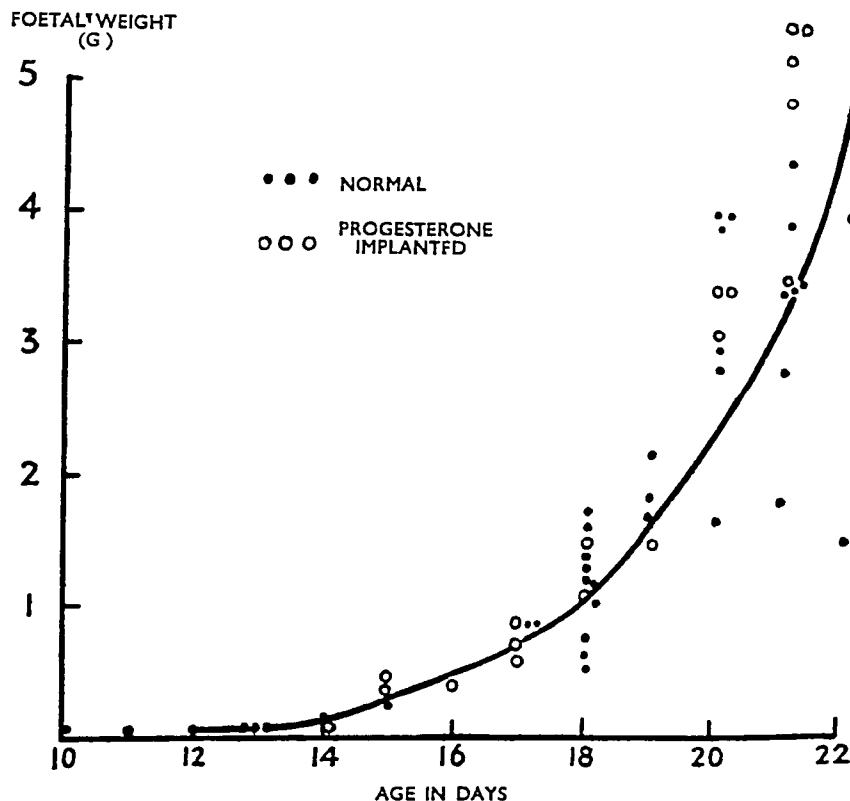
The presumption is that the lack of adequate iron supplies in pregnancy has depleted reserves in the embryo, which depletion reveals itself in the postnatal period when the diet is naturally short of iron. Two things lend weight to this surmise, first the demonstration by Zaleski (1886) that in

the dog the liver of the embryo at full term has 391 mg of iron per 100 g. of dry liver, compared with 43.78 mg per 100 g in the adult. In the human, at least two-thirds of this iron are stored during the last three months of intra-uterine life (Hugounenq, 1899). If there is a shortage, it is to be expected that this big storage might be defective without any signs in the circulating blood. That a shortage is normally liable to occur is evident from two things: first, that infantile anaemia can occur on a milk diet unless other sources of iron are supplied (Mackay & Goodfellow, 1931); second, the anaemia is worse on cows' milk than on human milk, which is to be expected since 1 litre of human milk has 3 mg of iron and of cows' milk only 0.8 mg per litre.

Fullerton (1937) has demonstrated, however, that in the human the liver is not the main store of iron. The human foetus has in its liver at birth only 50 mg of iron, in other tissues 70 mg, but in the blood 330 mg. The position in the human embryo is clearly different to that in the dog foetus. Pommerenke, Hakin, Bale & Balfour (1942) have studied transmission of iron to the human foetus by "labelling" it with radioactive iron. It was given to the mother by mouth before delivery at term, and blood was removed from her and from the umbilical vein for estimation. It appeared in 40 minutes within the foetal circulation, which indicates a fairly rapid passage across the placenta at full term. In another series it was administered before therapeutic abortion in cases between the 2nd and 7th month of pregnancy. The radioactive iron was then estimated in the different tissues of the aborted embryo. The largest deposition was in the foetal erythrocytes, considerably less in the foetal liver, and negligible in other foetal tissues.

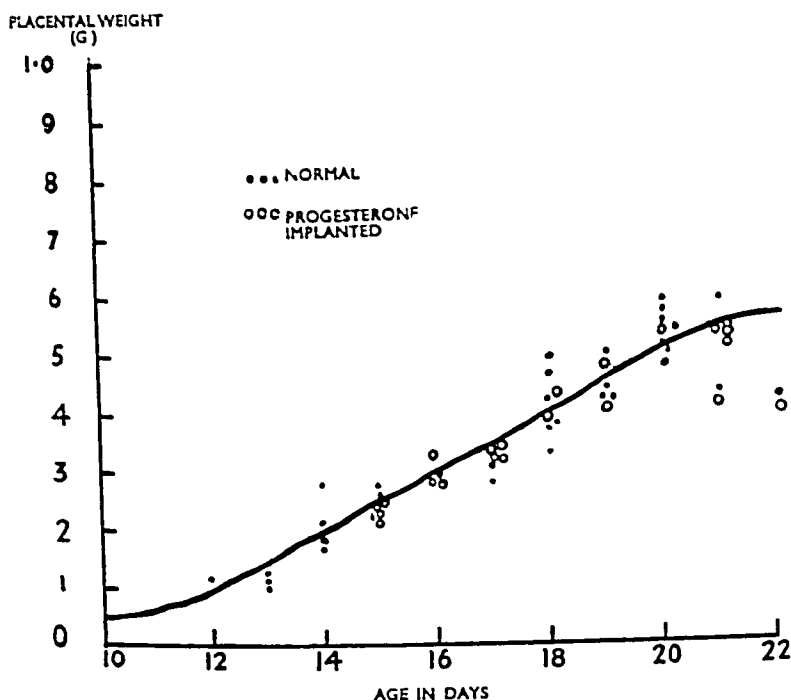
It is quite clear, therefore, that so far as iron is concerned, the total present in the diet of the pregnant animal or mother determines the severity and duration of the anaemia which occurs during the first year of life. Where there is a shortage, the mother shows an active anaemia of the hypochromic type and the infant shows no anaemia. Apparently the higher metabolic rate of the embryo has grasped the available iron at the expense of the low metabolic rate of the mother. This is, however, not the whole story, since, within the embryo, the circulating erythrocyte shows no deficiency at birth. Apparently, however, there must be a deficiency in the liver in the case of the dog. Fullerton (1937), as has been said, regards the reserves of iron for circulating blood as being the blood itself and such outside sources as are available to it in the postnatal food supply, since the haemoglobin percentage falls from 145 to 86 at the 9th month and as low as 37 in infantile anaemia. For this reason he stresses the necessity of iron feeding of the infant, and doubts the value of iron supplementations in diet of the pregnant woman. In view of the findings of Strauss and Smallwood, it is doubtful whether Fullerton's contention can be wholly correct.

FIG 2 [RELATIONSHIP OF FOETAL WEIGHT TO FOETAL AGE IN THE RAT]



From a series of experiments in which the action of progesterone upon the foetal weight was assessed. The curve is the normal growth-curve for untreated rats. Note the rapid increase in the last two days. Full term is 21-22 days.

FIG 3. PLACENTAL WEIGHT AT DIFFERENT DATES IN THE RAT



From the same series as the last. Note the marked slowing in the last two days of pregnancy. In many species (including the human), the placenta loses weight at this stage.

The development of erythrocytes is not, however, a matter only of iron. Wills (1931, 1933) has shown the megalocytic anaemia of pregnancy is curable by the administration of the haematopoietic factor of the liver or the extrinsic factor present in marmite [a vegetable concentrate]. This condition occurs in Indian women on a diet lacking the extrinsic factor. There is no record of the state of the blood of the infants born of the anaemic mothers, a matter of considerable importance. If the extrinsic factor be viewed in the light of Hammond's theory as a nutrient, for which the foetal haematopoietic tissues, with their high metabolic rate, successfully compete against maternal demands, the megalocytic anaemia of pregnancy in the mother is a logical sequence.

The same approach can be applied to minerals other than iron. Protein is a component of blood, both in the haemoglobin and in the circulating plasma proteins. In severe malnutrition the plasma proteins decrease. In pregnancy the mother stores much protein, both in her uterine and her extrauterine tissues. Protein needs to be increased in pregnancy for foetal requirements. This is recognized in all modern dietaries for pregnancy. Copper, likewise, is needed in the maturation of the normoblast to the erythrocyte. It is stored in the foetal liver in the pig (Wilkerson, 1934), and in both the goat and human (Ramage, Sheldon & Sheldon, 1933), so that at full term its concentration is double that of the adult liver. Unlike iron, however, copper is not deficient in the mother in pregnancy; the level of copper rising in the maternal blood from an average of $0.205\% \pm 0.025$ to $0.275\% \pm 0.075$ (Sheldon, 1932). In other words, a deficiency

of copper is a factor less likely to cause postnatal anaemia in the infant.

Factors in Calcification

Calcium, on the other hand, with phosphorus and vitamin D, have been demonstrated as necessities which, if not supplied by the maternal diet in quantities above the normal non-pregnant adult requirements, will, because of the high demands of the foetal bone-growth, be inadequate not only for maternal metabolism but also for the postnatal development of the infant.

A decrease in the calcium and phosphorus in the diet of pregnancy causes no decrease in the embryo of the dog (Dibbelt, 1910, Zuntz, 1919), but even on a normal diet this is achieved at the expense of a loss of calcium from the maternal tissues (Sherman & Macleod, 1925), unless extra calcium and phosphorus be given (rat Toverud & Toverud, 1929a, human Toverud & Toverud, 1929b, Booher & Hansmann, 1931). Maternal caries (M. Mellanby, 1929) and osteomalacia (Maxwell, 1930) and, with the osteomalacia, intrauterine rickets, can also occasionally occur and are curable by cod-liver oil together with calcium and phosphorus. A rachitogenic diet in puppies can cause rickets more effectively

if it is begun, as the maternal diet, in the intrauterine period (E. Mellanby, 1926). The Toveruds (1929) showed that while equilibrium is reached in the non-pregnant adult on a diet containing 0.7 g of calcium and 1 g of phosphorus, in pregnancy this needs to be raised to 1.6 and 1.7 grams respectively, while Sontag, Munson & Hoff (1936) brought forward evidence that, within limits, foetal ossification is independent of the diet, provided that adequate supplies of vitamin D are present. This confirms the findings of Abel (1931), who showed, however, that excess causes hardening of the foetal skull-bones.

It is clear, therefore, that the early high rate of metabolism of bone-growth *in utero* makes demands on the nutrients required, which are satisfied at the expense of the mother's tissues unless supplied in extra amounts in her diet. Further, if the supply is only partially met the infant shows signs of deficiency in post-uterine life. In the case of these nutrients, however, unlike iron, there is a rich supply in the maternal milk, provided that the diet of the mother in lactation is adequate. But the foundation is laid *in utero*.

What has been said about iron, calcium, and phosphorus applies also to all other nutrients in varying degree. The diet must be balanced in quality and adequate in all respects, with fortification in certain foodstuffs. It needs to be fortified for the mother's requirements, particularly with certain amino-acids such as methionine. At the moment we have no direct evidence of the necessity of these supplements for foetal development or for its postnatal life, though it would

be absurd to expect its requirements in growth to be less than the adult requirements

It is necessary here to refer to three important experiments conducted on supplementation of the mother's diet during pregnancy. None was so complete, owing to the difficulties of human experimentation, as to be conclusive, but all three were significant. In South Wales and Gateshead it was found that supplementation with vitamins, milk and iron decreased still-births and neonatal deaths (Williams, 1939). Ebbs, Tisdall & Scott (1941) compared good diets with poor and with supplemented diets, and found that the addition of fruit, eggs, milk and wheat-germ decreased morbidity markedly, while in 1942 the People's League of Health showed that supplementation of normal diets with minerals and vitamins decreased prematurity and slightly increased birth-weight. All these effects were accompanied by improvements in the maternal condition during pregnancy.

Placental Permeability

In investigations of the placental permeability there is a limited number of observations which bear on the question of the postnatal development of the infant.

The most important is that it is normal for the placenta to show atrophic changes which, towards full term, result in approximation of the two blood-streams, with diminution and disappearance of the intervening layers in varying degree in different species (Grosser, 1925, Mossman, 1937). This results in a big increase in permeability in the last months of intra-uterine life, with a concomitant passage of the foodstuffs. This is well shown in curves relating the intra-uterine age to the foetal weight and the placental weight, and by the passage of radio-active sodium in different species of increasing permeability (Flexner & Gellhorn, 1942).

The second point of importance is that the passage of

foodstuffs is often against the physical gradient of concentrations. This raises the question of mechanism of placental transfusion which, with molecular weights over 350, appears to involve mechanisms other than simple diffusion (Anselmino & Hoffman, 1929), and particularly so with colloids and particles. However, there is no doubt that in the last three months of intrauterine life the placenta becomes very permeable to certain organisms and certain colloids, though so far as the evidence shows, apart from lipids, none passes in nutritional quantities. In the case of proteins, the passage of nutritional quantities is by amino-acid diffusion (see Huggett, 1941a). Proteins can pass across in colloidal state, but only in "immunological" quantities. This applies to certain viruses, to certain toxins and antitoxins, and to agglutinins, the most striking being the passage of the Rhesus factors.

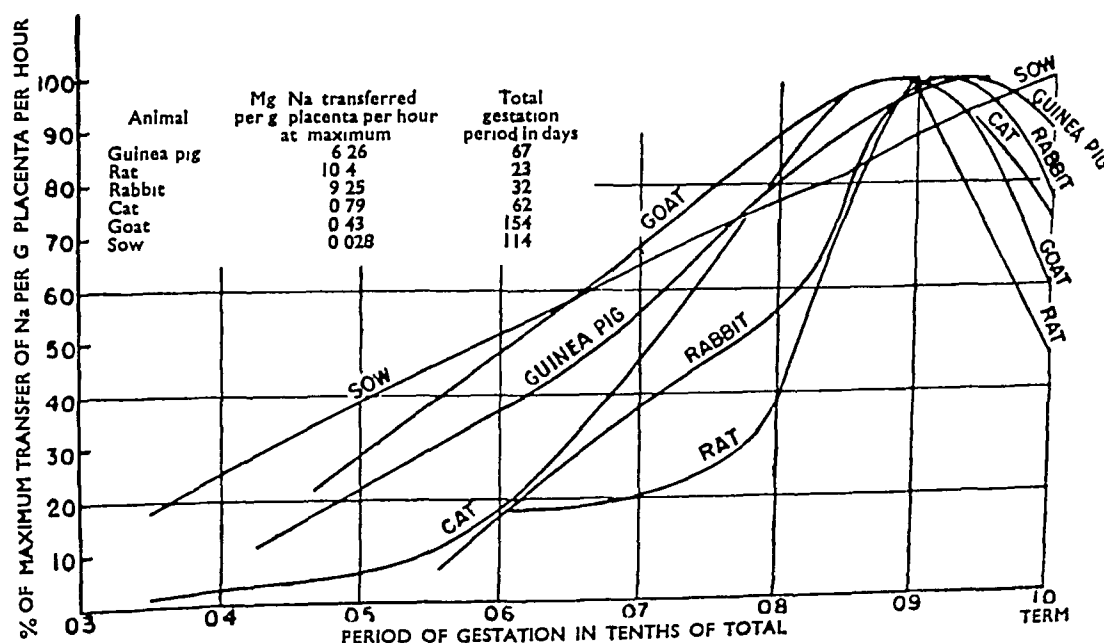
This passage of immunological quantities of proteins through the placenta is relevant to the known permeability of the placenta to traces of essential factors, notably the water-soluble vitamins and the hormones. The whole question, therefore, is of considerable importance in the nutrition of the infant. Variation in the permeability of the placenta in different individuals is suggested by two observations. In the first place, the incidence of erythroblastosis foetalis in Rhesus-positive infants of Rhesus-negative mothers should be 90-100%. In actual fact only 5% of these infants develop erythroblastosis foetalis. Haldane (1942) suggests that in only 5% of placentae is the permeability so great that the isoagglutinins can traverse to the foetus. Secondly, Dienst showed in 1905 that if the attached placenta at full term was perfused with methylene blue, the dye appeared in the maternal urine in only 20% of cases.

While in both these cases there are alternative explanations, the possibility of differential permeability affecting the

nutritive supply of the infant at the stage when its reception of nutrients is maximal is an important aspect of the question of the influence of prenatal nutrition on postnatal development. What is required is the optimum flow of nutrients to attain vigour without extremes of weight.

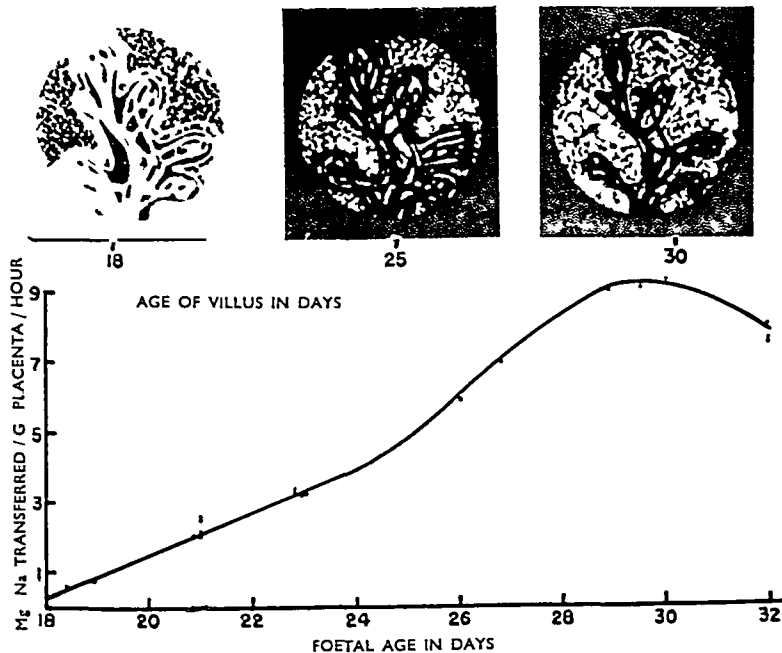
It is desirable here to draw attention to two points made by Barcroft (1944) in this connection. He emphasizes the importance of placental size and, secondly, of its opposition to oxygen passage, and ventures the opinion that the size of the foetus is limited by the size of the placenta and its opposition to oxygen passage. What limits the placenta we do not know.

FIG 4 RATE OF SODIUM TRANSFERENCE ACROSS THE PLACENTA (Flexner & Gellhorn, 1942)



This shows the relative placental permeability in different species at different dates during pregnancy

FIG 5 CORRELATION OF PERMEABILITY AND PLACENTAL STRUCTURE AT DIFFERENT AGES IN THE RABBIT (Flexner & Gellhorn, 1942)



The tissue intervening between the maternal and foetal bloods—decidua and trophoblast—atrophies in pregnancy in varying degree in different species (most in the rabbit) with an accompanying increase in permeability with a change in the last tenth of pregnancy

It must be admitted that we have no sure means of assessing the nutritive condition of the infant *in utero* either directly or through a study of the maternal condition. This is not surprising, as it has been shown that foetal death or removal without placental death does not remove the signs of pregnancy, which progresses to full term, resulting then in the delivery of the placenta, with the concomitant signs of puerperium (mouse Newton, 1935, monkey van Wagenen & Newton, 1943).

The nearest we can go is to recognize that maternal loss or subnormality of weight, or decrease in functional efficiency or decrease below the physiological normal for pregnancy (where known)—all or any of these stigmata are danger signs of a condition liable to impair the health of the foetus *in utero* or the infant after birth.

In conclusion, we can emphasize that a balanced diet in pregnancy duly fortified where necessary, is essential for foetal and infant health quite apart from the benefit conferred on the mother herself.

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BLINDNESS AND VISUAL DEFECT OF CONGENITAL ORIGIN

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The immense advances in public health administration during the past century, and in chemotherapy during the past decade, have greatly reduced the incidence of infectious disease generally and of ocular infections in particular. In consequence, other causes of disease have assumed a proportionately greater significance. This is strikingly seen in a comparison of the causes of blindness in children at different periods during the past sixty years.

Decline of Ophthalmia Neonatorum and other Infective Causes of Blindness

In 1884, the then newly-established Ophthalmological Society of the United Kingdom carried out a collective investigation on the causes of blindness amongst inmates of blind-schools and institutions for the blind. Ophthalmia neonatorum was found to be the responsible cause of blindness in 30-41%. These percentages cover inmates of all ages and, as the liability to blindness increases with age, it is clear that considerably more than 30% of blindness in children must have been caused by ophthalmia neonatorum.

In 1922, the Board (now Ministry) of Education found that, in the schools for blind children in England and Wales, 28.5% of the scholars had been blinded by this affection. A parallel survey carried out in 1944 showed that in the space of twenty-two years the proportionate incidence of blindness from ophthalmia neonatorum had declined to 9.2%. It is likely that within a decade blindness from ophthalmia neonatorum, once a dominant cause, will have become a rarity in the United Kingdom, for it is exceptional now for an infant to be blinded by this affection. In the four years 1941-44, only three babies in the whole of England and Wales have become blind from this disease.

Though no strictly parallel figures are available, there is

much suggestive evidence that a decline of the same order as seen in ophthalmia neonatorum has occurred in other infectious eye diseases leading to blindness and visual defect. Congenital syphilis has declined greatly in frequency, and in consequence blindness and visual defects from this cause have also greatly diminished. Phlyctenular ophthalmia, too, has declined, and so has blindness from the various infectious fevers. As a result, the proportionate incidence of the different causes of blindness has become greatly affected. Whilst in 1922 congenital and hereditary lesions, including myopia, accounted for 37.3% of the causes of blindness in children, in 1944 no less than 67.6% of all blindness was produced by these affections.

In England and Wales the number of blind children between the ages of 5 and 16 has shown a steady decline since 1923. In that year the rate per 100,000 children in that age group was 36.4. By 1943 the rate had fallen to 20.3. Table I shows the decline as recorded at intervals during that period.

TABLE I INCIDENCE OF BLINDNESS IN CHILDREN AGED 5-16 YEARS, ENGLAND AND WALES, 1923-43

Year	Population aged 5-16 years	No. of Registered Blind aged 5-16 years	Rate per 100,000	
1923	7,477,143	2,723	36.4	
1925	7,306,761	2,720	37.2	
1927	7,385,359	2,554	34.6	
1929	7,262,590	2,438	33.6	
1931	7,166,056	2,355	32.9	
1933	7,246,446	2,089	28.8	
1936	6,890,730	1,853	26.9	
1938	6,694,300	1,676	25.0	
1939	Population	1,619	24.2	Based on 1938 population figures
1940	figures not available	1,499	22.4	
1941	for	1,425	21.3	
1942	publication	1,369	20.5	
1943		1,355	20.3	

That decline is, of course, to be explained mainly by the decline in the infectious causes of blindness. It carries this significant implication: as to-day some two-thirds of all blind children are afflicted from congenital and hereditary lesions, the rate of blindness per hundred thousand is likely to fall below the present 20.3, but within foreseeable time the rate will have become stabilized at the somewhat reduced level, for present-day methods of operation and treatment do not materially affect the congenital and hereditary lesions. A clear appreciation of the underlying factors in this group has therefore become of immediate and practical importance.

Terminology and Classification of Congenital Eye Defects

It is unfortunate that our very terminology of the congenital and hereditary lesions is confused. This confusion

reflects, of course, our ignorance of the scope of the problem. The term congenital blindness has no precise meaning. It is sometimes used as synonymous with a neonatal infection, such as blindness arising from ophthalmia neonatorum, or from birth injury, sometimes it is used to indicate a transmitted maternal infection, such as syphilis, and it is also used to designate blindness from genetic causes. By usage rather than by precise definition, blindness from such infectious disease as ophthalmia neonatorum and congenital syphilis is generally not included in assessments of blindness of congenital and hereditary origin. The tendency has been to confine the term congenital blindness to that arising from malformations and genetic infections. Thus, however, is not strictly valid, for there are other factors besides these two in congenital blindness. Nor may it be assumed that whatever be the case with malformations, blindness from genetic affections always manifests itself at birth. Such a characteristic genetic affection as retinitis pigmentosa may not cause blindness until well on in adult life, or even beyond.

An unsatisfactory terminology does in itself introduce confusion, but it is unlikely to be replaced until adequate knowledge throws up better terms. The first essential in any clear appreciation of the significance of the factors operative in congenital causes of blindness and visual defect is, therefore, a more detailed study of the group of affections that to-day makes up some two-thirds of all causes of blindness in children. As yet only tentative and indirect explorations have been carried out.

Suggestive data are obtained from an analysis of the causes of blindness in infants up to five years of age admitted to the Sunshine Homes for Blind Babies. During the period 1920-43, 600 babies were admitted to these Homes conducted by the National Institute for the Blind. No less than 261 (43.5% of the total) were blind from clearly-defined malformations or congenital affections. "Congenital anomalies" (not more clearly defined) were responsible for 78 cases. Frankly congenital malformations, such as microphthalmos and buphthalmos, accounted for 47 and 24 cases respectively. Cataract of congenital origin was responsible for 48 cases, whilst no less than 24 cases were due to glioma of the retina, presumably bilateral.

It is difficult to sort out from this mass those that were genetic from those that were maldevelopmental in origin. Moreover, it is possible that some lesions grouped as endophthalmitis of infective origin might be due to transmitted maternal infection, as it is also likely that some of the cases of optic atrophy not included in the group of congenital lesions, might be congenital in origin. A significant feature of the findings in this study is that only one infant is noted as blind from retinitis pigmentosa, a disease that is undoubtedly genetic in origin and, though not manifest at birth, must be considered as congenital.

It is obvious that the very limits of congenital factors of blindness and visual defect have not been defined. For the moment one can only fall back on more or less valid generalizations. It is possible to distinguish in broad outline the following groups:

1 *Malformations* Congenital malformations have a wide anatomical range, extending from such a rare occurrence as congenital anophthalmos to relatively minor anomalies of the eye. Even the minor anatomical anomalies may have serious import. An abnormally-formed disc, or an ill-developed fovea, may cause gross visual defect. Most of

the congenital anomalies have clear clinical features, as characterized by the names of microphthalmos, buphthalmos, coloboma iridis, coloboma of the choroid, coloboma at the macula, congenital cataract, subluxation of lenses, and other designations. Congenital nystagmus is in a category by itself, for often no anatomical defect can be observed, but it is possible that, in some cases at any rate, there is lack of development of the fovea.

The aetiology of all these conditions is obscure. In days gone by congenital syphilis was frequently blamed, and "intrauterine inflammation" served as an alternative aetiological diagnosis. That many of these cases are genetic in origin is obvious from the intensive genetic studies that have been published on these anomalies, but frequently no genetic basis can be established. There is lack of evidence in many cases of any dominant transmission, or of recessive manifestation, consanguinity is unusual, and a goodly proportion of these anomalies are "sporadic", even if each of these anatomical lesions has been observed as a genetic feature.

Though much work has been done on the experimental induction of ocular anomalies by changing the prenatal environment of the embryo, it cannot be said that experimental embryology has been particularly successful in elucidating the nature of these lesions. None the less, it is established that experimental congenital cataract can be induced by hypocalcaemia in the pregnant rat. Some evidence for a clinical parallel is also available.

One puzzling feature in these congenital ocular anomalies is their frequent association with systemic malformations. Subluxation of the lenses is apt to be seen in arachnodactyly, aniridia may be associated with syndactyly, and even lobster-hand and -foot. Macular coloboma in one particular family was associated with apical dystrophy of the hands and feet, in another family, anomalies of the skin and hair were present with macular dystrophy. Deficiency in dental enamel in cases of congenital cataract finds a ready explanation in the common underlying hypocalcaemia at a critical period in intrauterine development, but it is difficult to see a developmental basis for such a freak association as aniridia with lobster-hand and -foot, or macular coloboma with apical dystrophy of the terminal phalanges. Conceptions like status dysraphicus help to clarify the position somewhat in such conditions as arachnodactyly, but it cannot be said that they do indeed throw much light. Genetic explanations, such as particular genes influencing a variety of characters, have much theoretical validity, but detailed knowledge of the multiple potentialities of genes is still sadly lacking. The confusion is not eased by the fact that known intrauterine infections can also exert widespread effects and produce weird combinations of anomalies.

2 *Abiotrophies* In contrast to the gross anatomical changes seen in the congenital malformations, is the wide group of ocular lesions in which there are no structural anomalies at birth, but which are none the less determined congenitally. Retinitis pigmentosa has already been mentioned as an example of this group, but there are many other less-common affections of this type. The large group of macular dystrophies, the familial forms of choroidal sclerosis, and the corneal dystrophies, are all well-established examples. A tissue that is apparently normal at birth, and may indeed function normally for a number of years (sometimes for a variable number in different families) shows dystrophic

changes, generally of a progressive character, and frequently ending in blindness. Both dominant and recessive forms of most of these conditions are recognized, and their congenital nature is obvious from their hereditary character. The designation of abiotrophy for this group of conditions has been criticized, the criticism is valid on etymological grounds, but not particularly helpful. It is of some importance to draw a sharp line of demarcation between the structural anomalies present at birth and the congenitally-determined affections.

The abiotrophies are probably much more common than is generally supposed. There is good reason for regarding the high degrees of pathological myopia as examples of abiotrophy. It is certainly a clinical fact that the complications of high myopia develop not at the time the myopia itself originates—in childhood and adolescence—but in late middle life, when there is no mechanical stress of growth to disturb the choroid and retina. Though the evidence is not conclusive, there is much to suggest that some forms of cataract and optic atrophy occurring late in life are essentially abiotrophic. It is arguable that some clinical conditions that are designated as senile degenerations of the eye are essentially late abiotrophic manifestations. Genetic evidence in support of this view is not difficult to obtain in almost any of the "senile degenerations" of the eye.

3 *Phakomatoses*. A group of conditions, of which tuberose sclerosis is a characteristic example, has features that link them with both the abiotrophies and neoplasms. A structure which is apparently normal at birth may develop changes which destroy both its function and the life of the patient. The tumours in tuberose sclerosis and neurofibromatosis behave in this manner, their effect is widespread and variable, as these tumours have a wide anatomical distribution. It is possible that so far only the more severe phakomatoses have been recognized, but that the condition, in its minor forms, with its minimal mother-spots (whence the name of phakomatosis), is common. The congenital origin of the phakomatoses is shown both by their genetic behaviour and by the congenitally-present phakomata.

4 *Neoplasms*. It is tempting to speculate on the relationship between the phakomatoses and the congenitally-determined (or congenitally-present) neoplasms such as glioma of the retina. As yet no close connection between the two has been established. None the less it is clear that glioma of the retina has a marked hereditary tendency with an irregular dominant mode of inheritance. A number of pedigrees extending over two generations has been published, and there is one on record extending over three

generations. Glioma of the retina is estimated to occur once in every 33,000 births. The high mortality of these tumours presupposes a high mutation-rate to maintain equilibrium in distribution.

5. *The lipid dystrophies*. Though relatively uncommon, these dystrophies are of considerable theoretical importance. Those having ocular implications are infantile and juvenile amaurotic idiocy, Niemann-Pick disease, and Christian-Schüller disease. Like other abiotrophies, none of these is manifest at birth, but that they are congenitally-determined is shown by their genetic behaviour. The significance of the lipid dystrophies lies in the fact that they form the one group of abiotrophies in which biochemical changes have been found, and in the case of the Christian-Schüller disease, these have indicated possibilities for therapeutic control.

6. *Intrauterine infections*. Apart from congenital syphilis, which is the classical example of a transmitted maternal infection producing widespread lesions present at birth, or supervening later in life, there are now at least two more recognized infections that are not held back by the placental barrier. Maternal toxoplasmosis can produce extensive changes in the nervous system of the offspring, as also a fairly characteristic central choroiditis which leads to blindness. More recently the virus of rubella has likewise been shown to be responsible for extensive lesions, of which congenital cataract and fundus changes are not the least striking.

The problems of intrauterine infection are fundamentally those of the environment of the growing embryo, and of the nature and variety of malformations that changes in such an environment may produce. To what extent minor lesions and functional derangements appearing later in life—as distinct from gross congenital anomalies—may also be caused by intrauterine infection must still be a matter of speculation.

* * *

If to-day some two-thirds of the causes of blindness in childhood are recognized as due to congenital and congenitally-determined causes, it must be admitted that there is little concrete knowledge as to the relative significance of the many causes of congenital and congenitally-determined disease. There is even less knowledge of the role of congenitally-determined factors in the development of anomalies later in life. A vast field of endeavour lies open. A century of effort has produced the present-day control of infectious disease. The exploration of the problems of congenital and congenitally-determined disease will require an effort no less intense, and the results may be commensurate.

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THE GENETICS OF CANCER

A Short Review of Experimental Findings

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The conception of an interaction of several factors in the genesis of the cancer process is not a new one, but it has received increasing support as a result of the researches of the last decade. Of these factors, genetic constitution has been shown to play an important part in animals, and there can be no reasonable doubt on general grounds that the conclusions drawn from animal experimentation are applicable in modified form to the pathology of human cancer. The genetic aspect of the cancer problem has been investigated in many laboratories, but the pioneer work of establishment of strains of mice with differing cancer incidence was done largely by American biologists and geneticists. The mouse has proved to be a valuable animal for these experiments, owing to its short life-span, its high reproductive rate, and its special susceptibility to a visible cancer, namely, of the breast.

Three difficulties arose in applying the Mendelian law to cancer

1 No animal can be assumed to be cancer-free, whatever its age at death, in other words, there is apparently no upper limit to the cancer age. This difficulty has been emphasized by Gorer (1937), who gives the following example: "Suppose we have three mice of which one dies of mammary cancer six months old, the second dies cancer-free at 15 months, and the third dies of mammary cancer at two years, what can we say of the genetic constitution of the cancer-free mouse?" There seems to be no means of overcoming this difficulty, but the failure to recognize it invalidated much of Slye's work.

2 Mammary cancer strains do not group themselves into "high" and "low". Incidences ranging from 0 to approximately 100% are described in genetically pure stocks. This fact in itself is sufficient evidence that mammary cancer cannot be caused by the action of a single gene. Thus comparisons must be based on populations, rendered as homozygous as possible by continued brother-sister inbreeding (Little & Gorer, 1943, p 318).

3 Experiments involving crossing between high and low cancer strains always give the result that the F_1 mice derived from high cancer females show a high breast-cancer rate, whereas in the F_2 mice derived from low cancer females the incidence is low. This fact, first pointed out by Lathrop & Loeb in 1918, has been amply confirmed by other workers. A good summary of the position is given by Burrows (1945, p 352), who points out that the degree of susceptibility in the offspring of a low-cancer strain mother crossed with a high-cancer strain father is passed on to the F_2 generation.¹

Influence of Bittner's Milk Factor

The conclusion to be drawn is that the existence of one or more extra-chromosomal factors gives the female parent a much greater influence upon the offspring than that of the male. It seemed natural to seek this factor in the generative system, and though a considerable volume of work was done in transferring fertilized ova from the uterus of high cancer to low cancer mice, it soon became apparent that the extra-chromosomal influence lay in the milk (Bittner & Little, 1937). Since this time, a vast amount of work has been done, especially by Bittner, in an attempt to discover the nature of the "milk-factor" and the conditions under which it acts. A complete account of this work cannot be attempted here, but summaries are already available (Andervont, 1945b, Burrows, 1945, p 355). But the following well-established facts may be noted.

a Females of all high cancer strains foster-nursed by low cancer mothers show reduction in mammary cancer incidence. The degree of reduction depends upon how soon after birth the babies are removed from their own mothers. There is some indication that reduction is maximal if the babies are removed from the uterus at term (Andervont & McEleney, 1941).

b Females of low cancer strains foster-nursed by high cancer mothers show increase in mammary cancer incidence. The degree of increase varies with different strains and in different laboratories (Miller & Pybus, 1945).

c Susceptibility to the milk factor begins to decrease after birth, but this can be overcome by giving a large dose—e.g. by using milk factor derived from dried mammary cancer tissue (Dmochowski, 1945).

d Transmission of the milk factor may be obtained not only by the milk, but by inocula of living tissues (spleen, thymus, mamma, but not liver) or whole blood. In spite of its wide distribution, this factor appears to be concerned only with the formation of tumours of the breast.

e Both the reduced liability to breast cancer brought about by deprivation of the milk factor, and the increased liability induced by its addition, can be transmitted to subsequent generations. These very remarkable facts supply evidence that multiplication of the factor occurs during the life of the mouse which has once received it (Andervont, 1945a). Genetic factors may be concerned in the ability to transmit or propagate the milk factor (Heston, Deringer & Andervont, 1944-45).

f Male mice which have received the milk factor and are subsequently oestrogen-treated develop breast cancer (Bonser, 1944). The Strong A strain seems to be especially refractory in this respect.

Before the discovery of the milk factor it had been established that oestrogenic stimulation was concerned in the genesis of mammary cancer in mice. This subject was fully reviewed by Gardner (1939).

Three Factors affecting the Incidence of Breast Cancer

The theory has thus been conceived that three factors are necessary for the genesis of breast cancer: an agent in the milk, oestrogen, and genetic constitution. Some evidence exists (Bittner, 1944) that the latter is transmitted as a single dominant factor, but it is also possible that multiple genetic factors may be concerned, one being linked

¹ (F_1 denotes the first filial generation produced by crossing two unlike individuals, and F_2 the second filial generation produced by mating two members of the F_1 generation.—Ed.)

with the gene for brown coat colour Van Gulik & Korteweg (1940) brought evidence to show that the genetic factor might work partly through strain-difference in susceptibility of the genital organs to oestrogen. They found that the high breast-cancer strains tested had genital organs less sensitive to oestrogen than low breast-cancer strains, and thus postulated that a greater quantity of oestrogen would be produced in them in normal conditions.

The question of dosage of the various factors must also be considered. For example, Bonser, Stickland & Connal (1937) were able to induce 5 breast cancers in 32 oestrogen-treated CBA females, in which milk factor is not normally present nor do breast tumours occur spontaneously. It would seem that the heavy dosage of oestrogen used was sufficient to initiate the cancer process in the absence of milk factor. The possibility also exists that the milk factor may vary in potency in different strains. The proof of this would require the administration of milk factor from a number of high cancer strains to low cancer mice of one strain kept under controlled conditions in one laboratory. This has not so far been done.

An obviously important aspect of this question is whether similar factors are concerned in the genesis of breast cancer in species other than the mouse, and especially in man. Evidence of a familial tendency to mammary cancer based on the incidence in near relatives of both cancer and non-cancer patients, was presented by Norwegian and Dutch investigators (Waalder, 1932, Wassink, 1935). This has not been confirmed in England (Passey, 1942). The method of assessment of cancer deaths in the relatives of the basal patients was, however, different in England from that in Norway and Holland, and this may account for the difference in the findings.

The demonstration of the interaction of three factors in such heterogeneous material as the human race is not likely to prove an easy task. Some interesting suggestions are made by Little (1941-42) as to the type of experiment which might be undertaken. Occasionally, exceptional opportunities occur for the study of high breast-cancer rates in certain families (Handley, 1938, Wood & Darling, 1943). This type of information is, however, of less value than that obtained from the more laborious and difficult studies undertaken by Waalder, Wassink and Passey. It is of interest to note that in Passey's series of 600 women with breast cancer, it has not been possible to trace a family in which the mother and the grandmother have both suffered from cancer of the breast (personal communication).

In 1944, Blank published a preliminary report of an extensive survey of the literature of the biological background of cancer until the end of 1941. This author concluded that there does exist in humans a general inherited predisposition, whether of susceptibility or of refractoriness, to tumour formation, but that other factors exist, most probably inherited independently of a general disposition, which govern the localization of the disease. If general susceptibility and inherited favourable internal environment are combined in an individual, these factors may be strong enough in themselves to lead to the formation of cancer. In addition, where general susceptibility is great in an individual, even relatively slight irritation by external agents may lead to neoplasia.

Greene (1939) described two types of breast neoplasia in two family groups of rabbits and concluded "that heredity

played a fundamental role both in the occurrence of the tumors and in the determination of the tumor type."

Chemical Carcinogens

An interesting development in the study of the interaction of several factors in the genesis of breast cancer has come from the use of chemical carcinogens in place of the milk factor. Bonser (1940) and Bonser & Orr (1939) observed the development of breast adenocarcinomas at the site of subcutaneous injection of methylcholanthrene in lard in mice of low cancer strains. One strain (IF) was more susceptible than a second (CBA). Mice of both these strains develop breast cancer when given milk factor from the RIII strain. Orr showed later (1943) that the methylcholanthrene could be administered by the intranasal route, the IF strain again being more susceptible than the CBA. The effect of the carcinogen was considered to be a distant one, the possibility of absorption through the nipple being eliminated by the use of oestrogen-treated male mice, in which nipples are not present. Administration by the cutaneous and intraperitoneal routes (Orr, 1944-45) was also effective. Bonser has recently observed (unpublished observation) that 2-acetyl-amino-fluorene administered by stomach-tube to mice of the IF and CBA strains is capable of inducing breast cancer, the IF strain being more susceptible. There is thus evidence that a chemical carcinogen can replace the milk factor, but that strains vary in their response. Whether this difference is genetic in the Mendelian sense has yet to be discovered.

Cancer of Internal Organs

Thus far, the factors which have been discussed are those concerned in the genesis of a visible, easily studied, and frequent form of cancer, namely mammary cancer. More difficult to analyze are the factors concerned with cancer in internal organs, but such studies have been stimulated (a) by the great variety of carcinogenic agents which has become available in the last decade, and (b) by the development of a large number of pure lines of mice. Two methods of approach are possible. Spontaneous cancer in a particular organ may be studied in different strains and experiments can be designed to alter its incidence, or a substance with known carcinogenic properties may be tested upon a number of strains and differences in the resulting cancer incidence observed. The use of these methods has been of great value in relation to tumours of the testis, liver, lung, adrenal, bone, stomach and skin.

Frequent interstitial-cell tumours of the testis have been observed in oestrogen-treated male mice of at least four inbred strains (Bonser, 1944), whereas they occur but rarely in other strains so treated. Such tumours do not occur spontaneously in the four strains which are susceptible to oestrogen. Gardner (1943) hybridized mice of strain A (susceptible) with mice of two other non-susceptible strains, and in 61 male hybrids found three spontaneous interstitial-cell tumours of the testis in mice living to a great age. As the hybrid mice lived considerably longer than their strain A parents, it seemed possible that increased longevity might have "afforded an adequate period for the materialization of inherent tendencies that might be elicited precociously in oestrogen-treated animals." The author postulated two influences essential for the inception of such tumours, namely, the tumoral environment maintained by oestrogen.

injections, and a genetic predisposition. A further example of the effect of prolongation of life was afforded in an experiment in which mice of the RIII strain foster-nursed by CBA were treated with the oestrogen triphenylethylene (Bonser, 1944). By this means, mammary tumours (which lead to early death in non-fostered mice) were suppressed and about one-third of the RIII mice which survived 50 weeks of treatment developed interstitial-cell tumours of the testis.

Spontaneous hepatomata occur fairly frequently in mice of the CBA and C3H strains, which were derived from a common stock (Strong & Smith, 1936, Gorer, 1940). They occur occasionally in other strains. Not all pathologists are agreed that these lesions are true tumours, but as metastases have been described and the tumours can be transplanted (Edwards, Dalton & Andervont, 1941-42), there is good reason for regarding them as neoplasms. Males are more commonly affected than females. When mice are treated with certain chemical carcinogens, e.g. 2-amino-5-azotoluene (Shear, 1937), carbon tetrachloride (Edwards & Dalton, 1942-43) and 2-acetyl-amino-fluorene (Armstrong, Bonser & Suckland, unpublished observation), the incidence of hepatomas in nearly all the strains tested is increased but, in general, the degree of increase varies with the carcinogen rather than with the strain. In the experiment of Armstrong *et al.*, however, strain limitation was very obvious.

When tumours of the lung in mice are considered, the true nature of the lesion is much more in doubt. These tumours appear at a late age as multiple tiny nodules, usually subpleural in position. They grow slowly and in many cases are not a cause of death. They are usually regarded as being derived from alveolar or bronchiolar epithelium, they are sharply circumscribed and do not metastasize. Even if not neoplastic, they undoubtedly occur spontaneously with great frequency in certain strains (80% in the A strain). Little & Gorer (1943) state that Lynch & Bittner agree that the susceptibility to these lesions is dominant and that it is probably determined by a single gene. Murphy & Sturm (1925) showed that if tar was applied successively to different areas of skin, a high incidence of lung tumours of this type occurred. Since then, a vast amount of work has been done, first by Lynch and later by Andervont and his co-workers, in studying the effects of many carcinogens on many strains (Andervont & Shimkin, 1940-41). Two conclusions were reached, namely, that the appearance of these lesions is a very sensitive index of carcinogenicity, and that the susceptibility of mice to induced pulmonary tumours is linked with their susceptibility to similar spontaneous tumours. Susceptibility is fairly completely dominant in most crosses, and more than one gene is concerned (Heston, 1942).

A very interesting series of spontaneous bone sarcomas was described in the NBT strain by Pybus & Miller (1938). These tumours occurred earlier and more frequently in females than in males. In recent years the incidence in both sexes has fallen considerably, from some unknown cause which is under investigation. When oestrogen was administered to mice of this strain, and the changes in the bones were compared with mice of strains with low bone-tumour incidence (Miller, Orr & Pybus, 1943), the following conclusion was made: "While it is clear that oestrinization alone does not give rise to bone sarcomata, there is reason to believe that it can act as an adjuvant agent when the determining factor or factors are present." The latter factors would presumably be genetic.

Occasional spontaneous adrenal cortical adenomas and carcinomas have been described in mice of both sexes (Woolley & Little, 1945a), but there is so far no strain with a high incidence of these tumours. Woolley, Fekete & Little (1940) described strain differences in both sexes in the degree of adrenal cortical hyperplasia following early gonadectomy. Two strains, dba and C3H, with a high incidence of mammary carcinoma, had more extensive adrenal cortical hyperplasia and accessory sex organ development than the C57 black strain (low incidence of mammary cancer). More recently, using the extreme dilution strain (JAXce), Woolley & Little (1945b, 1945c, 1945d) have shown that gonadectomy at birth of females and males results in the development of adrenal cortical carcinomas in all the mice surviving for a sufficient period of time. Evidences of strain differences in this type of tumour will be awaited with interest.

Epithelial tumours of the alimentary canal are very rare in mice, but Stewart & Andervont (1938) found that mice of Strong's I strain all developed an adenomatous lesion of the gastric mucosa by approximately eight months of age. The neoplastic nature of the tumour is in some doubt. A further reference to cancer of the stomach is made below. Attempts to induce gastric neoplasms in mice of numerous strains by means of carcinogens injected into the stomach wall were successful (Stewart & Lorenz, 1942-43), most of the tumours arising from the glandular portion of the stomach, though a few may have arisen from the squamous portion. There was no evidence of strain limitation.

Skin Tumours

No strain of mice has yet been described in which spontaneous tumours of the skin are at all common. The application of carcinogenic agents to the skin was, however, until about fifteen years ago the chief means of inducing cancer in the laboratory. It had been noted that in any batch of heterogeneous mice so treated there was a very great difference in time of appearance of the first and last benign tumours. Bonser (1938) attempted to select lines of mice derived from parents showing the characteristics of early and late wart formation. The technical difficulties encountered in the latter attempt prevented a successful result, but a strain of mice was established (termed IF) in which skin warts resulting from the use of several carcinogenic agents appeared earlier than in any other strain tested. Contrary to expectation, the warts, although appearing earlier, took longer to become malignant. This strain has been maintained at Leeds and was retested in 1945 (unpublished observation). The characteristics of early wart formation and delayed development of malignancy have been considerably modified.

Descendants of Methylcholanthrene-treated Mice

An entirely new approach to the study of the genetic nature of cancer susceptibility has been initiated by Strong (1944-45). Wishing to imitate in experimental animals the variable genetic background of man, this author hybridized mice of the CBA, JK and N strains by means of tandem crosses and treated the descendants with methylcholanthrene for eight generations. Under these controlled experimental conditions, a great number of neoplasms was produced in mice descendant from the methylcholanthrene-treated mice but themselves untreated. In many cases the cancers were multiple. The author concludes that biological variability

(as determined by genetic determiners) is concerned in the various types of cancer found in mice and possibly also in man. A selected strain (NHO) derived from the methylcholanthrene-treated hybrids and showing a wealth of new neoplastic diseases now becomes available for further research. It is expected that one of these diseases, namely, cancer of the stomach, will be of especial value for experimental work, in view of the prevalence of this type of cancer in man.

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From the foregoing description it will be obvious that the threshold has only just been reached in the search for the factors which are concerned in the genesis of tumours in organs other than the breast. When it is remembered how complicated are the reactions of relatively homogeneous inbred animals living under controlled laboratory conditions, it will be realised how difficult the task is likely to prove of evaluating the part played by genes, hormones, diet and other extrinsic factors in the genesis of human cancer.

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MENTAL DEFECT: RECENT RESEARCHES

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The problem of recognizing and defining what constitutes mental defect in contrast to normal mentality presents few difficulties when the deviation from the normal is gross, as in cases of imbecility and idiocy. Subjects whose mental capacities lie on the borderline between normal and abnormal are very difficult to assign to one class or the other. Cases considered defective on the basis of educational standards

alone, and not physically abnormal, are described as "subcultural" by Lewis (1933). Other designations, "physiological", "residual" or "acclinal", which have been used with the same connotation, serve to distinguish the low-normal variants from the "pathological" types in which mental defect is associated with definite physical disease or malformation.

The "subcultural" or "acclinal" cases, which outnumber the others in the proportion of three to one, are more or less coincident with the group termed "feeble-minded" in England and "morons" in the United States. The recognition of these cases and the ascertainment of their frequency in the general population depends upon applying standardized intelligence-tests to children. Surveys have been carried out by various observers in random populations to determine the range of intelligence. The Northumberland survey (Duff & Thomson, 1924) of 13,000 school children and the surveys of Scottish children (Scottish Council for Research in Education, 1933) are notable examples. Roberts, Norman & Griffiths (1938) tested nearly all children in one district, and thereby obtained a very accurate estimate of the

nature of the distribution of intelligence in this sample of the community

All these surveys showed that there was no natural line of demarcation between normals and defectives. A proportion amounting to about 2% of children can be counted defective on the basis of tests administered, but only a few of these cases are actually sent to schools for special education, and less than one-twentieth are placed in institutions. The defectives selected for institutional care or training are mainly those with severe defect. Many of those with milder degrees of defect, who are segregated in this way, display also antisocial behaviour.

Institutional Surveys

One of the simplest methods of discovering the different types of diseases associated with mental retardation is to examine large numbers of institutional cases. The first large group to be intensively studied was the series of 327 defectives classified by Goddard (1914) in the United States. Representative surveys, made by Larsen (1931) on 1,000 cases and by Wildenskov (1934) in Denmark, were followed in Britain by a survey of 1,280 cases by Penrose (1938) and in the United States by a similar survey of 347 cases by Halperin (1945). In all these investigations, attempts were made to sort out the different causes by clinical examinations and enquiry into family histories.

The earlier workers tended to separate a small group of acquired, secondary or exogenous cases from the whole, and then to suppose that all the rest were due to heredity of a simple kind. Recent work, however, has shown that such simplifications do not express the facts correctly. The comparatively rare cases in which disease or injury can be shown to be the chief cause of the mental defect do not exhaust the effects of environmental influences, which may be part-causes in a very large number of instances. Moreover, although a few rare types of defect are due to single genes, usually recessive, the mode of inheritance, by means of which intelligence of the subcultural level is produced, is very complex and multifactorial.

Prenatal Environment

In recent work on the environmental causes of mental defect, much attention has been given to prenatal influences. The very early stages of development must be involved in the malformation of mongolism, a clinical entity first recognized by a London physician, Langdon Down (1866), which affects about one in every 700 births. Advanced age of the mother is undoubtedly a significant factor in the aetiology, and this has been shown by statistical enquiry. The study of twins has been, since Galton's time, a favourite means of estimating the relative importance of nature and nurture, and it has been pursued in the hope of elucidating the cause of mongolism. Ford & Frumkin (1942) made a detailed study of the finger- and palm prints of a pair of mongol twins. The discovery by Cummins (1936) that, in such cases, the dermal ridges show typical peculiarities, which made diagnosis both of the disease and of the monozygosity of these twins easier, emphasizes the possibility of a genetical factor in the causation besides the effect of maternal age. On the other hand, morphological similarities found in monovular twins are not necessarily always due to common heredity. More significant, perhaps, are the differences. Hobbs (1941) described a remarkable pair of monovular twins, one of whom

was above average intelligence and the other almost an imbecile from birth though physically well-formed. The mental defect in the abnormal twin must have been due to some adverse prenatal influence.

Attention has been directed to the importance to the foetus of maternal health by observations on children whose mothers had rubella in the first half of pregnancy.¹ The original observations, made by Gregg (1941) in Australia, have been at least partially confirmed by later enquiries (Erickson, 1944). It is important, however, to remember that mental defect associated with congenital cataract is also found as a familial disease (Sjogren, 1933). Several infective diseases which may pass from mother to foetus and cause injury to the nervous system are now known. Ironside (1940) described an interesting case of juvenile paresis in one of a pair of fraternal twins of a syphilitic mother. Mental retardation in the affected twin was present since birth, typical neurological signs developed but no stigmata were present. Besides syphilis and rubella, the rare toxoplasmosis can pass from mother to foetus, and it causes progressive and widespread destruction of nervous tissue in congenital cases (Vail, Strong & Stephenson, 1943).

Allied to these observations are studies on the effects of therapeutic pelvic irradiation given to women in the early months of pregnancy. Goldstein & Murphy (1929) first brought forward evidence that foetal malformation could result from such treatment. Maxfield (1941) described a case of microcephaly, which might have had its origin in the radiation therapy received by the mother, and Murphy, Shirlock & Doll (1942) reported a somewhat similar case where mental defect in the child was associated with diplegia.

Clinical Types with Genetical Origin

Most cases of defect with congenital physical abnormality or progressive disease of the nervous system are of low grade and infertile. When the cause is hereditary, the simple dominant type of transmission from parent to child is thus unlikely to be observed. Recessive heredity is recognized by familial occurrence among brothers and sisters, whose parents are normal but more often consanguineous than is usual. Cases of probably recessive genetical origin can, in fact, be picked out by finding excess of parental consanguinity. First, however, the normal frequency of cousin-marriages needs to be determined. An investigation carried out in England under the auspices of the Medical Research Council and analyzed by Bell (1940) showed that the frequency of first-cousin parents among all types of hospital patients was 0.61%. Among the parents of cases who suffered from diseases treated at neurological hospitals, the frequency was about twice as high. The frequency of first-cousin parents among 1,280 institutional defectives was found (Penrose, 1938) to be 1.9%, and the corresponding figure obtained by Duff & Dingee (1941), in a Canadian survey of 2,082 defectives, was 1.1%. The excess of parental consanguinity in these large groups has been shown to be due to the inclusion of numerous rare clinical types of congenital disease which are inherited recessively.

Familial Cerebral Diplegia

Among the important types to which attention has recently been drawn, is familial cerebral diplegia, which has been studied by Bell & Carmichael (1939). On the basis of these

¹ [See Parsons (*BMB* 873) in this number—Ed.]

observations, Haldane (1941) suggested that the recessive gene concerned might be partially sex-linked. Stewart (1942), nevertheless, pointed out that there is a great variety of conditions which can be included among cases of diplegic defect, and that some may be due to foetal malnutrition.

Microphthalmia

Microphthalmia associated with mental defect, usually of low grade, is not very uncommon. It is a condition which lends itself readily to genetic investigation because of its easy recognition. A sibship containing four affected sibs, two imbecile twin males, and a male and female of normal intelligence, was reported by Kallman, Barrera & Metzger (1940). The parents were second cousins. This recessive type of inheritance contrasts with the sex-linked type exhibited by the cases described by Roberts (1937), one case of which was examined, post mortem, by Whitnall & Norman (1940). The optic nerves, chiasma, tracts, lateral geniculate bodies and one corticovisual area were found to be grossly deformed and the eyeballs completely disorganized.

Abnormal Lipoid Metabolism

A sibship containing six cases of the recessive juvenile amaurotic idiocy was described by Jervis (1941). The age at onset of symptoms in all instances was between 5 and 6 years. Norman & Wood (1941) described a congenital form of the disease, in which the only child of unrelated parents survived but a few days after birth, the brain showed extreme microcephaly with a lipoid dyscrasia and pachygyria. Cases of the dystrophy named "gargoylism" by Ellis, Sheldon & Capon (1936) have attracted attention from many observers. Ross, Hawke & Brown (1941) gave descriptions of four cases. Jervis (1942) described a family in which the cases were somewhat atypical, and argued that the disease was closely related to amaurotic idiocy. Halperin & Curtis (1942) have shown that gargoylism is due to a single recessive gene.

Phenylpyruvic-acid Excretors

The discovery, by Følling (1934) in Norway, of the urinary excretion of phenylpyruvic acid in certain imbeciles, stimulated a large number of researches in other countries. Cases have now been reported in England, France, the United States, Switzerland and Canada. In the analysis of 47 sibships, in each of which there was at least one case, Munro (1940) confirmed that the condition was recessively inherited, in 5 of these families the parents were first cousins. Pugh (1940) showed that such patients have an abnormally high degree of creatinuria.

An interesting experiment in the treatment of some of these cases was carried out by Bates (1939), who fed them on massive doses of thiamine, he was, however, unable to report any mental improvement. In the United States, further information about the nature of the biochemical abnormality involved has been obtained by studying blood sera and tissues. Kondritzer (1940) studied the precipitation pattern of serum proteins, and found a small but significant increase in the globulin fraction as compared with the normal. Analysis of the amino-acid content of tissue-proteins by Jervis, Block, Bolling & Kanze (1940), however, did not demonstrate any differences between normals and phenylketonurics. Jervis *et al.* (1940) also clearly demonstrated phenylalanine in the blood of such patients, confirming, by a new method, the results of the Norwegian investigators, whose recent work on the subject has been summarized by Følling, Mohr & Ruud (1944).

Some Rarer Conditions

More information has been accumulating recently about a variety of rare clinical conditions associated with mental defect. Cases of hyperostosis frontalis interna continue to be discussed in the literature, though the origin of the disease is still obscure; Stewart (1941) showed that the new bone formation in the skull is not due to brain atrophy. Ferriman (1940) discussed the irregularly-dominant type of inheritance found in oxycephaly and acrocephalosyndactyly. Both diseases, which are significantly associated with mental defect, are often sporadic in occurrence, especially acrocephalosyndactyly.

Mental defect associated with cutaneous naevi may occasionally appear in more than one member of the same family. A sporadic case was recently described by Ironside & Hill (1941). Multiple angiomas affecting the retina and cerebellum (Lindau-von Hippel disease) in 4 patients, one of whom had an affected parent, were described by Craig, Wagner & Kernohan (1941). Here, some cases may be due to new mutation.

Disagreeing with the views of some investigators who have considered myotonia atrophica to be inherited as a simple dominant character, Maas (1937) and Maas & Paterson (1943) pointed out that there is a large variation in degrees of severity in affected members of the same pedigree. This disease is evidently commoner than is usually supposed. The writers inferred, from analysis of material which covered 94 families, that the worst-affected cases appear in the latter part of the sibship, and they maintained the viewpoint, now somewhat discredited but still held by Ravin & Waring (1939), that the disease tends to become earlier in onset in each succeeding generation.

Unequivocal evidence of sex-linked inheritance in mental defect has not often been obtained. A type of severe mental defect associated with no outstanding physical abnormalities and believed to be due to a sex-linked gene was described by Martin & Bell (1943). A more convincing pedigree investigated by Allen, Herndon & Dudley (1944) showed a type of defect associated with muscular dystrophy to be confined to males and to be transmitted, for five generations, always through normal females.

Erythroblastosis Foetalis²

A new pathway in the investigation of the genetical causes of mental defect was opened when it was ascertained that erythroblastosis foetalis, which was already known to be the forerunner of mental defect in rare cases, was primarily due to antigenic incompatibility of the foetus with the mother with respect to one of the "Rhesus" antigens (Levine, 1942). Survivors of severe erythroblastosis are occasionally defective (Race, Taylor, Capell & McFarlane, 1943) and surveys have been carried out to discover whether antigenic incompatibility can be held responsible for defects of hitherto unknown aetiology. In spite of the suggestive results obtained by Yannet & Lieberman (1944), subsequent investigations have tended to show that Rh incompatibility is not a frequent cause of mental defect. Other antigens may, however, also be significant.

Psychological and Vocational Aspects

The hope of improving the mental capacities of defectives by subjecting them to special treatments or courses of training has been recently revived by some work in the United

² [See also Race (*BMB* 872) in this number—Ed.]

States Cutler, Little & Strauss (1940) studied the effect of benzedrine administration over long and short periods on the test scores of a group of mentally-retarded children. Immediately after administration of the drug, improved scores were obtained on the Knox Cube form boards and the Porteus Mazes. No permanent benefit, however, was derived even in patients whose treatments were continued for six months. A somewhat more optimistic view was taken by Moskowitz (1941), who believed that, in selected cases, benzedrine raised the ability to a point where educational training could be facilitated. Kephart (1939) believed that, by specific training programmes, the intelligence levels of borderline and high grade feeble minded subjects can be raised, his results, which were based on re test data, were striking, but seem to require confirmation in view of the demonstrable effects of practice on test-performance (McIntosh, 1944). If re-testing is carried out at long intervals, such as 10 years, these objections do not apply, and it is interesting to note that, in a study of 85 institutional epileptic patients re-tested at intervals varying from 9 to 14 years, at a Canadian hospital, no evidence of mental deterioration was found except in three psychotic cases (Falk, Penrose & Clark, 1945).

Mental deficiency has presented some special problems in consequence of the war. An investigation, among British Army personnel, of the relationship between skin diseases and mental capacity was made by Hodgson (1941). Here, subnormal intelligence, as judged by the Matrix tests, was found prevalent in all groups referred for skin conditions, especially infestation (scabies and pediculosis) and venereal disease. On the whole, later observations (Rollin, 1943) confirmed these findings.

Much work has been done on the mental abilities of cases referred by the armed forces because of psychiatric or behaviour problems, but no great proportion of such cases has usually been found defective. Sutherland (1941) reported

that the mean mental age in 45 cases of war neurosis was 12 years on the Matrix tests and 14 years on the Binet scale. Anderson (1940) pointed out that defectives may sometimes make more satisfactory naval ratings than their more intelligent brethren, provided that no psychopathic features are present.

The general principle, however, in most services has been to exclude defectives at the outset, as likely to give unsatisfactory service. Esher (1941) considered all cases below a mental age of 7 years and 11 months, which corresponds to an intelligence-quotient of 50 to 60, untrainable. In a sample of 100 cases specially studied, referred by the British Army, he found that 80% had relatively high mental ages, i.e. from 9 to 11 years. Esher made a correction for a decline in intelligence-test scores with advancing age, and further recommended that, in considering school records, careful attention should be paid to the fact that the criteria of promotion vary in different schools. The use of the Kent Test for screening purposes has been widespread because of its convenience and brevity. Rudolf (1941) examined the performances of 367 adult defectives, and showed that male responses differed somewhat from female responses, using Earl's adaptation. It is evident that, although the standards of intelligence required for success in the armed services and success in civilian life are not exactly the same, the experience in the use of tests during the war will have important future bearings upon the concept of mental deficiency in civilian life.

It must not be inferred, moreover, that the mentally defective could not adapt themselves to wartime strains. Benjacer (1940) reported that institutional cases co-operated well in civilian defence work and useful constructional tasks. They showed no more liability to panic than normals, and were very susceptible to efficient leadership, their reactions to war varied from blissful ignorance to moderately intelligent patriotic interest.

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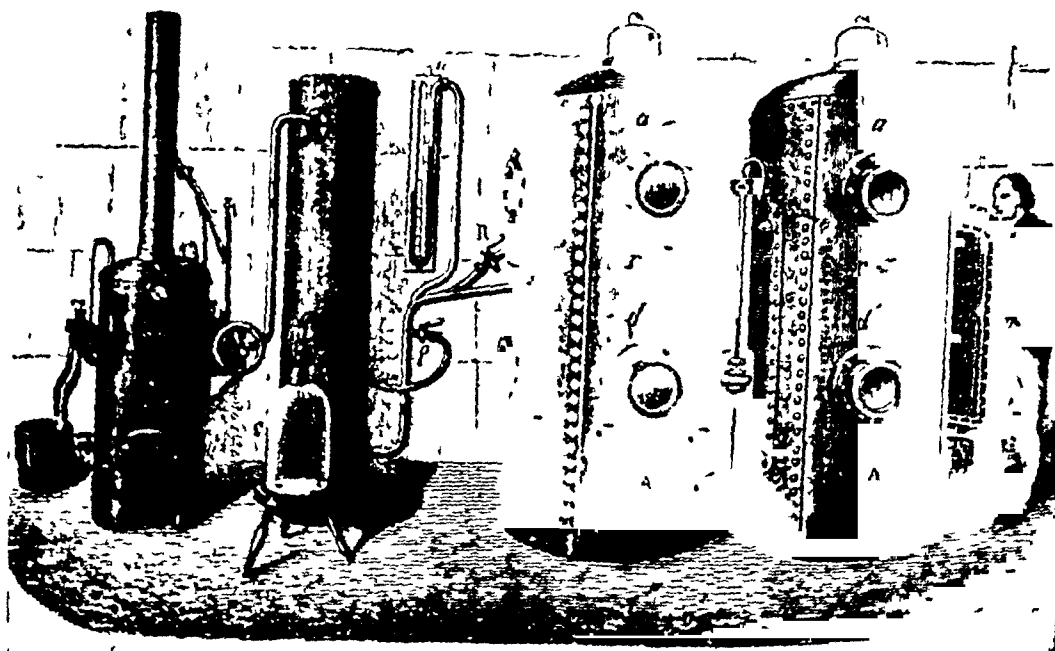
History, Bibliography and Comment

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Paul Bert's *La Pression Barométrique*

"It can be said of Paul Bert as it has of Vesalius, Harvey and Boyle, that the full significance of his work could not be fully appreciated until long after his death, but it is tragic that the chaos of a far-flung war was required to bring Bert's work into its full meaning and perspective. At a time when altitude physiologists and flight surgeons are being feverishly trained by all countries at war, it becomes of first importance to English-speaking peoples that the great classic of altitude physiology should be made available in the English language"

FIG. 1 PAUL BERT'S APPARATUS FOR STUDYING THE EFFECTS OF REDUCED PRESSURES



Press barom Fig 27, p 631)

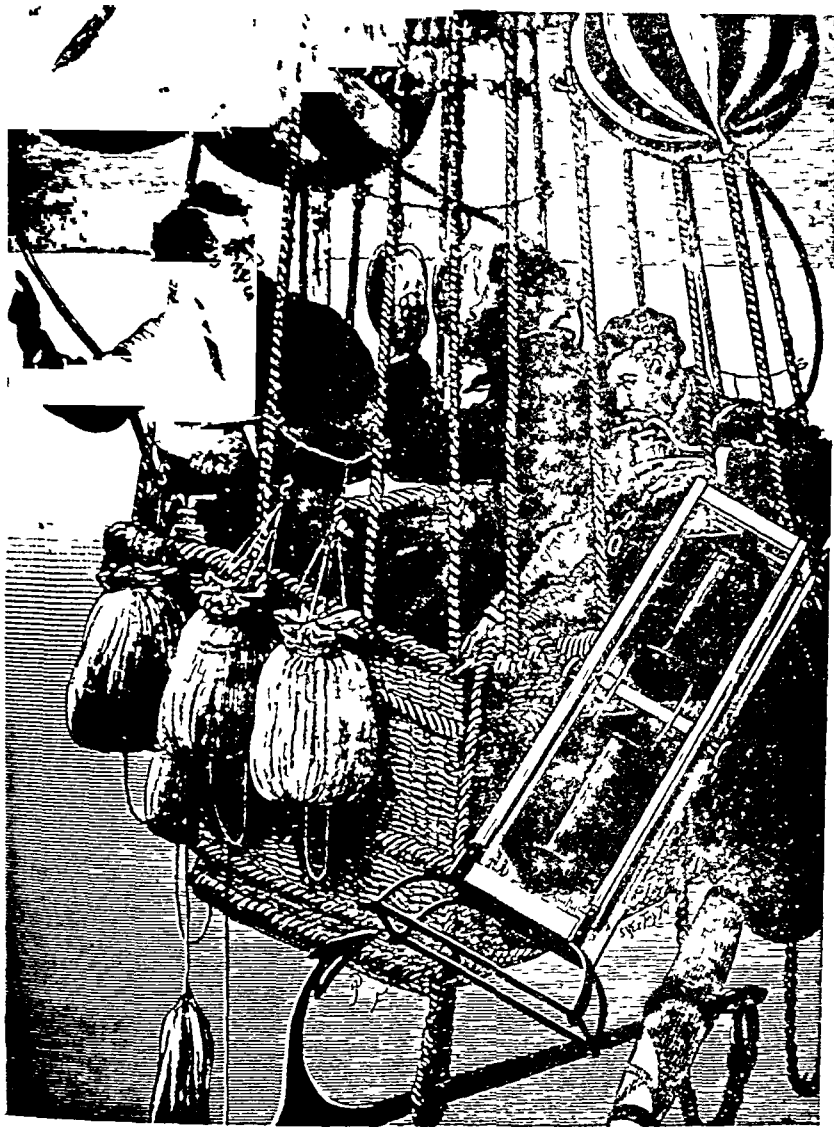
These are the opening sentences of the foreword by Professor John F Fulton to the English translation², published in 1943, of Paul Bert's *La pression barométrique recherches de physiologie expérimentale* (Paris, 1878). Professor Fulton is distinguished both as a physiologist and as an expert in medical history and bibliography, and it is therefore with special authority that he describes Bert's monumental book as "the very corner-stone of modern altitude physiology". Perhaps greater than any verbal tribute, however authoritative, is the fact that a physiological work published in 1878 should be of sufficient contemporary scientific value to be re-published in translation in 1943. For it was not because of its mere historic interest that the recent translation was published, but because the work contains a body of detailed information and discussion that is not available elsewhere. The author of a modern work¹ on aviation medicine has written

"Unfortunately this valuable work has been almost entirely overlooked and forgotten in our present day, yet one who aspires to a knowledge of aviation medicine must not feel that he has been successful until 'La Pression Barométrique' has been carefully read and absorbed"

And again
 "a great part of our so-called modern research in this field is nothing more than a repetition of his findings of more than 60 years ago"

In these decompression chambers, Bert exposed animals, and himself, to reduced pressures. It was also in this apparatus that Crocé-Spinelli and Sivel tested their reactions to a reduced pressure equivalent to an altitude of 7,300 m, just over a year before their fatal ascent in the *Zénith*. The cylinders A, A' are of riveted sheet iron, and are provided with glass portholes. In the narrow cylinder, a very low pressure (50 mm) could be attained. By throwing this cylinder into communication with the larger cylinders, an instantaneous reduction of pressure could be effected in the latter. In front of the narrow cylinder is a bell jar used for experiments on small animals. In the larger cylinders, thermometers are inserted at a, a', and cocks for taking air-samples at r, r', d, d', and s, s'. Manometers are shown at m, m'. At the extreme left, a steam engine which operated the pump is seen. Bert later replaced this with a gas engine.

FIG 2. THE FATAL ASCENT OF THE ZENITH



The early afternoon of 15 April 1875 Tissandier (centre) who some years previously (1870) had escaped by balloon to the provinces during the siege of Paris is tapping a barometer and taking a reading in response to an inquiry from Sivel (left). He tells Sivel that the reading is 300 mm (about 7 450 m altitude) and Sivel suggests discarding more ballast. The others agree and Sivel cuts the release cords of 3 sandbags. The balloon rises rapidly. Croce-Spinelli is seen on the right about to breathe oxygen from a wash bottle. The 3 striped bags are of greased goldbeater's skin and contain an oxygen air mixture. Because of the disagreeable smell of the bags, the gas was inhaled through wash-bottles containing water flavoured with benzoin. According to Tissandier the illustration above is an accurate representation of the scene. After Sivel had cut the release cords he and Croce-Spinelli sat motionless in the nacelle. Tissandier lost consciousness at 8 000 m. About $\frac{1}{2}$ hour later he awoke for a moment and found that Croce-Spinelli had also regained consciousness and was discarding more ballast. About $1\frac{1}{2}$ hours later Tissandier again awoke and found that the balloon was descending rapidly. Half an hour later and $4\frac{1}{2}$ hours after the commencement of the flight the balloon landed and Tissandier found that his two companions were dead.

Press barom Fig 86 p 1065)

Lest it be thought that it is only since the recent war that Bert has been discovered, it should be added that Haldane's *Respiration*⁸ the standard English-language work accorded him full recognition in the following words:

the foundations of our scientific knowledge of the physiological effects of low atmospheric pressures were laid broad and firm by the investigations of Paul Bert which were collected together in this book already so often referred to, *La Pression Barometrique*.

Paul Bert's conclusions remain valid up to the present day.

La pression barometrique contains viii + 1 163 pages and 89 figures and is divided into three parts: (i) Historical (522 pp), (ii) Experiments (418 pp), (iii) Recent Facts Summary and Conclusions (115 pp). There are also two short appendices: a list of figures and a table of contents. One of the outstanding impressions created by the book is its comprehensive thoroughness. In the remarkable historical part the author has found and collated references to every aspect of his subject. In his

preface he points out that he has exercised in his historical researches *les soins les plus minutieux* and that his object has been to bring together everything that has been written on his subject. In his bibliographical researches he tells us he has learnt how often a summary or translation may convert the affirmations of an author to negations. For this reason he has chosen to report the exact words of the authors cited. (As if in ironic confirmation of Bert's mistrust of second hand sources words is misprinted as works in the English translation of this passage.)

The historical part is divided into two main sections: (i) Diminished pressure and (ii) Increased pressure. Section (i) opens with a short survey of the lofty regions of the globe and then proceeds (Chapter I) to an enumeration of the effects of high altitudes reported by mountain travellers. The first region considered is South America and the reports range from those of the Spanish Conquerors to those of Bert's contemporaries including the Englishman Clements Markham. There follow the accounts of travellers to Central and North America.

Mount Etna, Teneriffe, the Alps, the Pyrenees, the Caucasus, Armenia and Persia, Central Asia, Africa, and the volcanoes of the Pacific. Chapter II is a fascinating account of balloon ascents, from the invention of the gas-balloon (the Montgolfier hot-air balloons are not included, as they did not attain significant altitudes). In Chapter III are considered relevant theories and experiments, down to Bert's own time, and Chapter IV is devoted to a summary and criticisms of observations and theories previously related.

The second section of the historical part—Increased Pressures—is also divided into four chapters, as follows. Chapter I is an extraordinarily interesting survey of the development of diving-bells and the diving-suit, Chapter II is an account of observations made by other writers on the effects of the moderately-increased pressures which physicians were using in Bert's time for therapeutic purposes.

The title of this chapter in the original is *Faibles pressions*. In the English translation, this is rendered as "Low pressures", whereas Bert defines *faibles pressions* as including pressures of 1-5 atmospheres. (It must be conceded that exception can also be taken to Bert's term.) Chapter III is a review of earlier experiments on and explanations of the effects of compressed air on living organisms, and Chapter IV is devoted to a Summary and Criticisms.

In the second part of the work, Bert describes in detail a comprehensive range of personal experiments on the effects of reduced, increased, and suddenly-changed pressures on various animals (including man), and also the effects of pressure-changes on plants, on putrefaction, fermentation, ripening of fruits, and on the "viruses" of vaccinia, glanders and anthrax. Davaine's work on anthrax had brought to Bert's notice the existence of small organisms—"bactéries"—in the blood of affected sheep, and Bert put to the test Davaine's theory that these organisms (*B. anthracis*) were the virulent agent of the disease. He submitted samples of infected blood to oxygen at high pressures, and found that it still retained its virulence for animals. On the incorrect assumption that the organisms must have been

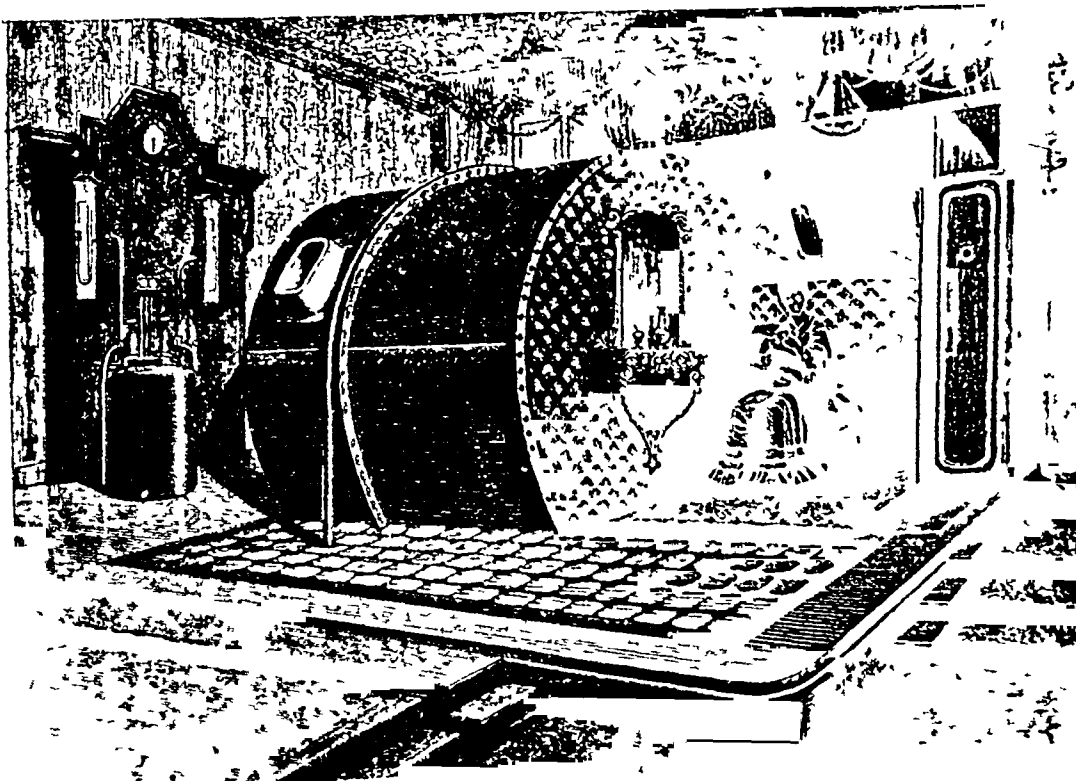
killed by the treatment administered to them, Bert asserts that they could not have transmitted the disease, although he limits his assertion to the particular samples of blood upon which the experiments were performed. History has proved Bert wrong on this small point, but he had what seemed to be a sound basis for his incorrect assumption⁴, and the outstanding characteristic of his work as a whole is that so much remains unchallenged and unsurpassed.

It is in the third part of his work that Bert includes, largely in the words of Tissandier, the sole survivor, the story of the disastrous ascent of the balloon *Zenith*, in which two of the crew of three—Crocé-Spinelli and Sivel—lost their lives from anoxia. A recent writer⁵ does less than justice to Bert in saying that he initiated his researches on anoxia "after the disaster in 1875 to the balloon *Zenith*". By this date his work had reached an advanced stage, and had been reported in a series of communications to the Académie des Sciences of Paris and in a preliminary monograph (1874).

On 9 March 1874, Croce-Spinelli and Sivel, intending to challenge previous claims for altitudes attained by balloon-ascent, called upon Bert and observed their own reactions to decompression in his "cloches à dépression". In this experiment the pressure was reduced to 304 mm Hg—equivalent to an altitude of 7,300 m. Both the balloonists experienced the disagreeable effects of atmospheric rarefaction, and both noted the favourable effects of the inhalation of oxygen from a rubber bag. In a subsequent experiment (30 March 1874), Bert was able to maintain himself in reasonable comfort, by continuous inhalation of oxygen, at a pressure equivalent to an altitude of 8,800 m. The maximum altitude reached by the *Zenith* during its disastrous flight was 8,600 m. Ten days after their test in Bert's decompression chamber, Croce-Spinelli and Sivel made their first high-altitude flight in the balloon *Etoile Polaire*, attaining a height of 7,300 m. They both found it necessary to inhale a mixture of oxygen and nitrogen, with which Bert had furnished them.

The fatal ascent in the *Zenith* was made on 15 April 1875, this

FIG 3 A PRECURSOR OF THE EXPERIMENTAL DECOMPRESSION CHAMBER;
FORLANINI'S "AEROTHERAPEUTIC ESTABLISHMENT"



Undiscriminating and empirically-based therapeutic measures are often the precursors of new fields of scientific inquiry. The "pneumatic medicine" of the late eighteenth century, involving the inhalation of newly-discovered gases, was succeeded after an interval by inhalation anaesthesia. In 1819, Gondret, a French physician, suggested that disease might be treated by the production of varying barometric pressures in a pneumatic chamber. In 1835, another French physician, Junod, constructed such a chamber for therapeutic purposes, and similar chambers were later utilized by physicians of many countries. The illustration of Forlanini's aerotherapeutic chamber is taken from *La pression barométrique* (p. 429). In 1892, Forlanini introduced artificial pneumothorax in the treatment of pulmonary tuberculosis. A sequence of ideas may be observed here: first, the subjection of the whole patient to varying pressures, second, the variation of the barometric pressure within the pleural cavity.

TERCENTENARY OF THE BIRTH OF JAMES YONGE SURGEON, 1646-1721

time with a third member of the party—Gaston Tissandier—who was the only one to return alive. Bert, who was at this time away from Paris, received a letter from Crocé Spinelli telling him of the projected ascent and of the amount of oxygen that was to be taken. Bert replied that far more oxygen than was proposed would be required, but the letter would seem to have arrived too late. The balloonists did not, in fact, exhaust even the limited supply of oxygen that they had taken with them, for when they attempted to reach for the life giving tubes they were powerless to move their arms.

The statement¹ that Bert 'built the first decompression chamber, in which low-pressure air conditions could be studied on the ground' is also misleading, as may be ascertained by a study of Bert's own book. In 1835, a French physician, Junod who had made observations of the effects of high altitudes in several mountainous regions, constructed a spherical copper chamber, 1.3 m in diameter, in which he studied the effects of moderate decompression in man. Junod's chamber was designed to serve therapeutic ends, and other French physicians contemporaneously engaged in similar essays in 'aerotherapy'. In Bert's time, such apparatuses were to be found in many European countries, and an 'aerotherapeutic establishment' had been installed by Forlanini in Milan.

In his foreword to the English edition of *La pression barométrique*, Professor Fulton includes some biographical particulars of Bert. He was born in 1833 and originally chose for his profession engineering, which he abandoned in favour of law. Changing his mind again, Bert took up the study of medicine, and graduated at the late age of 30. He was an ardent Republican and anti Clerical, and in 1881 he was made Minister of Public Instruction in the administration of Gambetta, who it may be recalled had escaped by balloon from Paris in 1870 during its siege by the Germans. In 1886, Bert went as Resident-General to Tongking in French Indo-China, where he died of dysentery a few months after his arrival, at the age of 53. It is noteworthy that the great body of work incorporated in *La pression barométrique* was carried out within the short space of 8 years (1869-1877).

The translation of the English edition is the skilful joint work of a linguist, M. A. Hitchcock, and her physiologist husband, F. A. Hitchcock, and they are to be felicitated upon the completion of a labour which must have been extremely arduous but which has been well worth doing.

Finally, is not the moment most opportune for a biography of Paul Bert? There could hardly be a more fitting subject, and we are tempted to wonder whether Professor J. M. D. Olmsted, who has already given us splendid biographies of François Magendie and Claude Bernard, might not consider the preparation of a study of the life and work of the third of this great line of French physiologists.

A H J

'How many prodigious things are there done in this last age, that to the former seemed impossible?' This might well be a question asked concerning the medical advances of recent years, but it was actually written by James Yonge (1682), the first to describe the flap operation for amputation the tercentenary of whose birth falls this year. He was born in 1646 at Plymouth, Devon, the son of John Yonge, surgeon, and his wife Joanna. By the time he was nine years old James could read and write, and in 1654 he entered the local grammar school. His stay there was short, for at eleven years of age he was at sea as apprentice to Silvester Richmond surgeon of the 'Constant Warwick', a naval vessel of 31 guns, manned by 150 men and commanded by Captain Robert Voysey. This ship acquitted herself well in action and on one occasion the surgeon's apprentice was nearly washed into the sea during a storm, but perhaps the most notable incident during his service aboard was a brush with pirates. The 'Constant Warwick' had been ten days off Land's End when she sighted two ships. It appeared that the larger vessel was from Hamburg and that the crew of the smaller craft was plundering her. The pirate craft ran inshore in an attempt to lure the 'Constant Warwick' aground in the shallows, but the warship gave chase, fired her guns and captured the pirate ship within sight of many people who had gathered on the shore to witness the fight (Anon 1849).

Samuel Pepys, the famous English diarist, records that he visited, in May 1661, a fine ship "called the Montagu" (Power 1931-32), and it was about this time that James Yonge was appointed surgeon's assistant aboard her. It was in the 'Montagu', in 1662, that he took part in the bombardment of Algiers. The fighting lasted six hours and the 'Montagu' lost her boatswain and another man while four men were wounded, one of whom subsequently died. Yonge recorded in his journal (Anon 1849, Munk, 1878) that he dressed the wounded and placed them on heaps of clothes for greater comfort. He also made their barley-water, boiled gruel, prepared fomentations and poultices and performed many other duties, including shaving and trimming for the surgeon was not yet separated from the barber. Later in the year James Yonge returned to England spending four months with a surgeon-apothecary at Wapping before going to Plymouth to work for his father. But his relations with his parent were not very amicable and in February 1663 he was bound for Newfoundland as surgeon to the 'Reformation', a small ship of a hundred tons. On his return he sailed in the following year in the 'Bonaventure' to the West African Coast, and it was during a subsequent voyage in this vessel that he was captured on 21 December 1665 by the Dutch. Imprisonment in Holland followed until he was exchanged early in 1667. He voyaged again to Newfoundland, but after fourteen years of naval service he resolved to settle in his native town. I hope it will be more quiet and less dangerous', he wrote in his journal (Anon 1849).

In 1670 while only in his twenty-fifth year but with a wealth of experience that would have sufficed most men for a lifetime, he started to practise in Plymouth. Cases soon came. A man fell from the topmast of a ship and fractured his skull from crown to ear. He recovered under Yonge's care, and despite the jealousy of colleagues, the new surgeon prospered. As the result of his marriage about this time to Jane Cramphorne whose family had influential connections, he was recommended as surgeon to the naval hospital. He was appointed but this was a circumstance that nearly cost him his life and posterity some interesting medical literature, as he almost died of spotted fever caught from his patients. In 1674 he became Surgeon-General of the Navy's deputy at Plymouth and his worldly success was assured.

It was about this time that he began to write and achieve a more than local reputation for in 1667 he sent an account to the Royal Society of Antony Williamson, who had a bullet in

¹ Armstrong H G *Principles and practice of aviation medicine* 2nd edition Baltimore, 1943

² Bert, P *Barometric pressure researches in experimental physiology* Translated from the French by M. A. Hitchcock & F. A. Hitchcock Columbus Ohio 1943

³ Haldane J S & Priestley J G *Respiration* Oxford 1935

⁴ Bert's work on micro-organisms is discussed and explained by W. Bulloch in *The history of bacteriology* Oxford 1938

⁵ Matthews B H C *The effects of high altitude on man* (The first of two Oliver Sharpey Lectures before the Royal College of Physicians of London March 1945) *Brit med J* 1945 2 75-80

LEIDEN AND EDINBURGH

A MEDICAL PARTNERSHIP

his trachea for three years (Moore, 1900) His most important work, which contains the first description of the flap operation for amputation, was published in 1679 in circumstances that were almost accidental He visited London with the Member of Parliament for Plymouth, a Mr Sparke, in 1678, where, "in an accidental congress of some surgeons" (Yonge, 1679), conversation turned on methods of arresting haemorrhage "I quietly allowed each to give his opinion", writes Yonge (Anon 1849), "when I demanded if they knew a thing that could incomparably stop hemorrhage of a wound, secondly, if they could cure amputated stumps by consolidation They confessed their ignorance, and laughed at the second as impossible, but I so explained and discovered myself, that they were extremely satisfied, and Mr Pearse gave me great thanks, and asked me to write more on it So I wrote my 'Curus Triumphalis Terebintho' " The description of the flap operation is appended to this work on turpentine

In 1682, he published "Wounds of the brain proved curable, the remarkable history of a child four years old cured of two very large depressions, with the loss of a great part of the skull," He describes a case he attended and quotes over sixty authorities to support his thesis that wounds of the brain are not mortal He wrote several other works during the last thirty years of the seventeenth century, but the two books described were his most important contributions to the literature of British surgery

On 23 May 1702, Yonge was admitted an Extra-Licentiate of the Royal College of Physicians of London (Munk, 1878) At his examination he was asked "what difference was between a Gangren and a Sphacelus", to which he replied "one was sideration of all the parts not curable but by amputation, the other of the fleshy parts and otherwise to be cured" He was then asked "the method of curing Gangren without amputation", to which he gave a satisfactory answer "When I received their Licence", Yonge writes, "they all complimented me and made me sit down among them, We sat 2 hours drinking good ale and claret, and talking sometimes of news and sometimes of art" (Moore, 1899) Later in the year, on 3 November, Yonge was elected a Fellow of the Royal Society

James Yonge was now a person of consequence in his native town In 1694, he had been Mayor of Plymouth, and it is interesting to note that in 1703 his patients numbered 444, of whom 14 died (Anon 1849) From this time onwards he lived in semi-retirement, but his last recorded duty was his most famous Sir Cloudesley Shovell, commander of the English fleet, was returning to England in "The Association" when his flagship was wrecked on the Bishop Rock near the Scilly Isles All the crew perished, the half-drowned admiral dying after being washed ashore His body, originally buried in the sand, was exhumed and brought to the citadel at Plymouth, where it was embalmed by James Yonge Thus he finished his professional career and in the seventy-sixth year of his age, on 25 July 1721 (Munk, 1878), James Yonge died and was buried in the church where he had been baptized, namely, St Andrew's, Plymouth

F Tubbs

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The geographical progress of medical education is one of the most remarkable phenomena in the history of medicine Scientific medicine, as opposed to magical healing, had its birth place in Greece From Greece, it passed to Rome and Alexandria, then by way of the Moslem Empire to Salerno, the first great medical school of Europe Salerno yielded precedence to Bologna and Montpellier, and eventually Padua became recognized as the leading medical centre At the Reformation the restrictions imposed upon Padua and other Catholic Universities provided an opportunity for the newly established university of Leiden (Leyden), which was open to all, irrespective of religion

From the date of its inception in 1575, Leiden University had a Faculty of Medicine There was a galaxy of distinguished anatomists, commencing with Peter Paaw, one of the founders of the school, and including Ruysch, who invented a method of injecting blood-vessels, Tulp, who was depicted by Rembrandt in "The Teacher of Anatomy" and who was the first to describe the East Indian disease beri-beri, and Bidloo, who wrote a textbook of anatomy, beautifully illustrated by himself Another early teacher at Leiden was Francis de la Boe (Sylvius), equally distinguished as an anatomist and as an exponent of clinical medicine, one of the first to teach clinically, by the bedside

The Leiden School, with its brilliant staff, attracted students from all countries As the teaching was in Latin it was intelligible to any person of education From England, Scotland, Ireland, and even America, students came to Leiden in increasing numbers Sir Thomas Browne graduated M D there in 1633, and from Scotland came a noteworthy trio, Sir Robert Sibbald, Dr James Halket, and Dr Archibald Pitcairne, who were appointed, jointly, in 1685, to the chair of Medicine in the Town's College, which later became the University of Edinburgh Archibald Pitcairne, the youngest of the three, who attained distinction for championing Harvey's discovery of the circulation of the blood, was appointed to the Chair of Medicine at Leiden, where he numbered among his pupils Herman Boerhaave and Richard Mead Mead became the leading London physician of his day, and Boerhaave, who succeeded Pitcairne, rose to be the most famous of all the Leiden teachers and one of the greatest physicians of all time

Another of Pitcairne's students was John Monro, a surgeon in the Army of William of Orange, whose son, Alexander Monro (primus), must share with Pitcairne the credit of founding the Medical School of Edinburgh John Monro envisaged a school for Edinburgh on the pattern which had proved so successful at Leiden, and he trained his son Alexander to be the first professor of anatomy and the first of a dynasty of three Alexander Monros who held the Chair for 128 years The first Alexander was a pupil of Boerhaave, and so was Sir John Pringle, the founder of modern military medicine

After the death of Boerhaave in 1738, Scottish students continued to frequent Leiden for many years Among them were four of the great family of Gregory, which produced no fewer than sixteen professors within a few generations One of the four was James Gregory, whose name is still associated with "Gregory's powder", and who succeeded his father as professor of medicine in Edinburgh

Thus did Leiden contribute in large measure to the foundation of the Edinburgh Medical School, and thus further links were added to the chain which had originally been forged so well by Archibald Pitcairne

Douglas Guthrie

TWO MEDICAL TRUANTS¹

The study of medicine is long arduous and expensive. Is it strange, therefore, if some medical men having spent their precious youth preparing themselves for a medical career and having lived casually for a while with their lawful wedded wife, the muse of medicine, should suddenly be led astray by the siren call of other muses henceforth to live a life of adultery with one of these? Some are forced into medicine to humour a paternal whim. Their profession soon becomes distasteful to them so that they play the part of truant gladly. Others undecided and vacillating in mind half-heartedly embark upon a medical career, which after a time ceases to allure them when they drift into some other pursuit. A few deliberately take up the study of medicine which they intend never to practise realizing the advantages of its scientific training as a preparation for other callings.

Impressive in its length variety and distinction is the list of physicians and surgeons who turned to literature art politics sport or murder for a vocation a profession a means of livelihood or a hobby. Of those who fell enamoured of the muse of literature some continued to practise their art writing in their spare time only while others forsook medicine almost as soon as they had qualified.

It so happens that two truants appeal to the commemorative mind this year. William Curtis who deserted medicine to become one of England's most distinguished botanists and William Findlay who in his hours of leisure and in his enforced retirement strayed into the pleasant fields of literature.

William Curtis, 1746-1799

Already as a boy Curtis showed his love for natural history by spending his pocket-money on botanical books. One of his greatest friends was Thomas Legg, ostler at the Crown Inn Alton a learned botanist in whose company he would roam the countryside. Such an intimacy for their son sober parents might have deprecated and ambitious ones have condemned yet hence the youthful Curtis imbibed that taste for natural knowledge which proved the source of his future fame and profit and above all of what is not always justly appreciated, his happiness (Abraham Rees *Cyclopaedia* 1819 x).

Born at Alton on 11 January 1746 the son of a tanner at the age of 14 Curtis was apprenticed to his grandfather a local surgeon apothecary. Six years later he went to London to finish his medical education becoming associated with a Mr Talwin of 51 Gracechurch Street whom he succeeded in business.

The apothecary was soon swallowed up in the botanist and the shop exchanged for a garden. In 1771 Curtis sold his practice and bought an acre of land in Bermondsey where he planted a botanical garden for his students for in addition to his medical practice he was demonstrator of practical botany at the medical schools. The following year he was appointed demonstrator of plants and *praefectus horti* to the Society of Apothecaries. In 1779 he acquired a more extensive garden at Lambeth Marsh which 10 years later the smoke of London spoiling his plants he moved to a site now occupied by the Brompton Hospital. His first published work was a pamphlet *Instructions for collecting and preserving insects* (1771). The first number of *Flora Londinensis* was issued in May 1775 and that of the *Botanical Magazine* (still published and edited at Kew on behalf of the Royal Horticultural Society) in February 1787 the former in his own words, bringing him praise and the latter bringing him pudding.

¹ [An account of many other medical truants is to be found in Lord Moynihan's *Linacre Lecture: Truants: the story of some who deserted medicine yet triumphed* Cambridge, 1936. This is an expanded version of the original lecture.—ED.]



WILLIAM CURTIS, F.R.S.
AUTHOR OF THE *FLORA LONDINENSIS*



An original Fellow of the Linnean Society (his is the third signature of the Roll Book) Curtis stimulated in his fellow-countrymen a popular taste for botany and horticulture. He was an entertaining companion, an accurate observer, a hard worker but a poor business man.

Afflicted with a disease in the chest supposed to be of a dropsical nature but which was rather perhaps an organic affection of the heart, he died at Brompton on 7 July 1799 at the early age of 53.

London has two memorials to Curtis: a plaque on the wall of the building in Gracechurch Street which occupies the site of the house where he practised as apothecary and his tombstone in the old Battersea Parish Churchyard. Arrangements have been made to renovate the stone and to restore its inscription.

An exhibition of *Curtisiana* at the Curtis Museum, Alton, was opened on 11 January by Mr John Gilmour, assistant director of the Royal Botanic Gardens, Kew.

Of William Findlay it has been claimed that in his *Ayrshire idylls* he did for Ayrshire what "Gavin Ogilvy" did for Forfarshire and "Jan Maclaren" for Perthshire. Born at Kilmarnock on 31 January 1846, the son of an engine-keeper, he inherited his literary gifts from his mother's brother, Archibald McKay, author of the ballad "My First Bawbee" and of the song "Be Kind to Auld Grannie". In 1866, he became a medical student at Glasgow, paying for his university education with his earnings as a carriage-painter and as an unqualified medical assistant during the vacations, and even missing a term or two. He was fortunate in having such teachers as the great Lister, Andrew Buchanan of blood-coagulation fame, and Sir William Tennant Gairdner. He graduated M.B., C.M. in 1870, taking the M.D. degree 8 years later. For many years he practised in Dennistoun, a growing suburb of Glasgow, until in 1906 an attack of coronary thrombosis forced him to retire and to devote himself entirely to writing. He died on 11 May, 1917.

Findlay's earlier works, both prose and verse, were published under the pseudonym of "George Umber". The real name, as well as the pen-name of the author appeared for the first time on the title-page of *Robert Burns and the medical profession* (1898). His *Carmina medici* (1902), which include such poems as "To Opium", "The Hypochondriac", "The Consumptive", "Sir Thomas Browne", "Sir W. T. Gairdner", "Glasgow Royal Infirmary", and "Therapeutics o' Gowf", were written mostly in the Scottish dialect, a glossary being provided "for the benefit of an ever-increasing number, I grieve to say, who have the misfortune to be unfamiliar with that tongue".

How highly contemporary poets thought of him is evident from the fact that they admitted him to membership of the exclusive Glasgow Ballad Club.

Of middle height and spare build, William Findlay impressed people with his shrewd kindness, his ready humour, the charm of his conversation, and his luxuriant hair and beard. Of his six sons, William became a noted portrait painter (now living in Los Angeles) and Leonard, an eminent paediatrician.

W R B

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THOMAS WAKLEY

Thomas Wakley (1795-1862), founder and first editor of the *Lancet*, the most famous of all medical journals, is the hero of a new biography by Dr Charles Brook. It is not the first occasion on which he has been the subject of the biographers, for the late Sir Squire Sprigge, a recent occupant of the editorial chair of the *Lancet*, wrote a charming book on *The life and times of Thomas Wakley*, and his biography was also published in serial form in the *Lancet* in 1895, the centenary of his birth.

In *Battling Surgeon*, Dr Brook paints a vivid picture of a great medical reformer who devoted his life to fighting the corruption prevalent in hospitals and medical schools a century ago. Many other notabilities of the period are included in this picture, making the book a valuable and interesting addition to the literature on medical history. In the opinion of the author, Wakley was the most important member of the medical profession in Britain during the nineteenth century, surpassing even Lister, who was "a mere pygmy by the side of Wakley".

This book reveals the great changes which have taken place in the last hundred years, for when Wakley received his medical qualification medical practitioners were not registered nor properly trained, there was corruption among the leaders of the medical profession, dissecting rooms were still supplied by resurrectionists and murderers, the treatment of hospital patients was often deplorable, and the adulteration of foodstuffs was scandalous.

When Wakley founded the *Lancet* he began to attack these abuses. One thing which particularly incensed many of the leading medical teachers of the time was his publication of their lectures, thus making available for sixpence a time (and with

much other information) lectures for which students paid five pounds a session. Attacks on Wakley followed, but he retaliated by publishing accounts of maladministration in the medical schools and malpractice in the hospital wards. This led to his involvement in much litigation, in which he was as often the loser as the winner. Much of the book is devoted to Wakley's battles in the courts and to the many other controversies in which he figured. Dr Brook has obviously gone to a considerable amount of trouble to consult original sources for his material, this makes the book all the more valuable, for many of these sources are now difficult of access. He has produced a fascinating chapter in the history of medicine in Britain. One reads again of the "row" in 1836, when the students from Guy's Hospital were suddenly refused admission to the operating theatre at St Thomas's (then adjacent to Guy's), a privilege previously allowed, of the burning of Wakley's house in Argyll Street by sympathisers of the Cato Street conspirators, and of Wakley's unscrupulous exposure of John Elliotson ("Dr Goodenough" in Thackeray's *Pendennis*). Elliotson sincerely believed in the curative value of mesmerism in certain conditions, but Wakley exposed him by a trick and almost brought to an end the career of one who was a friend of Dickens and Thackeray and who was held in high esteem by orthodox members of the medical profession. Wakley's work as a coroner and a member of Parliament is also fully recounted.

Dr Brook strives to show how the errors of the past can help to solve the problems of the future. He believes that "the age of the bottle of medicine and the smile as a doctor's sole stock-in-trade is passing, and we now look forward to the advent of a new and intelligent conception of health and disease. The fact remains that the family doctor is slowly but surely being squeezed out of existence. The establishment of publicly provided diagnostic, supervisory and treatment centres has deprived the family doctor of much of his former work, and the time does not seem far distant when the domiciliary midwife and maternity unit will entirely replace the hurrying and harassed doctor with his instruments all ready in his black bag."

A book of such importance as this deserves a better format and more expensive production. With so much of value between its covers, the lack of an index is a serious omission, affecting particularly the medical historian, who will assuredly consult this book. But perhaps the author, in keeping with the advanced views both of himself and Wakley, feels that his book should be produced at a price low enough to make his story available to all, and thus secure that appreciation of his hero which he feels is at present lacking. [For price and other details, see BMB 922.]

L T Morton

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THE APOTHEOSIS OF PARACELSUS

Paracelsus a genius amidst a troubled world, by Basilio de Telepnef, is, according to the dust-wrapper, the first step in a campaign to introduce "the true Paracelsus" to the English-reading public. It will be followed by unabridged translations of the works of Paracelsus. Basilio de Telepnef of St Gallen, short biographical study, published by Zollikofer of St Gallen, and most attractively printed. The author is a member of a Paracelsus Society which was formed recently at Einsiedeln, the birthplace of Paracelsus, and his study can be recommended as providing a short (93 pp) and easily readable study containing the essential facts of Paracelsus's life and work. In places, the style of the English translation is peculiar, but this does not constitute a serious obstacle to enjoyment.

Unfortunately, however, the author shows not the least pretence to objectivity in his treatment of his subject. His attitude is one of uncritical adulation, and he speaks, for example, of the "marvellous cures" of Paracelsus as if they were well-

attested facts. The allegation by Oporinus, Paracelsus's laboratory assistant, that Paracelsus was 'perpetually drunk' is described (p. 58) as 'the Basile calumny' and (p. 87) as 'the crassest instance of defamation by an ungrateful disciple', but we are not given the slightest hint of any reasons for disbelieving this allegation. It is surely not inconsistent with what we know of the violence and extremism of Paracelsus's personal character that he should often drink to excess. It is, at any rate, a little difficult to believe in him as a teetotaler, and if some passages in his writings were not composed in a state of inebriation they must have been the product of a mental state not far removed from it. However, if one may judge from this short study by de Telepnef, the new Paracelsus Society is the organ of a Paracelsus Cult. The most obscure verbiage of Paracelsus is holy writ, to be reverently searched for prophetic anticipations of modern scientific discoveries. Dr J. Strebel in a short introduction, refers to Paracelsus as 'this wizard' and says that 'the vitamins (sic) were clearly recognised by him'. In a similar vein, de Telepnef asks:

... were these clear notions of our modern 'discoveries' but visions of an enlightened seer, or (and much in Paracelsus's writings points to this latter conclusion) did some of the medieval alchemists—their secrets locked safely under the sombre vaults of dark laboratories, their dangerous knowledge inherited from the ancient magicians wisely guarded in occult circles far aloof from the profane world—did they in fact know infinitely more than we, in our pride, deem it possible?

This uncritical—and almost irrational—Paracelsus worship is not a new phenomenon. In 1837, a German writer, Quitzmann wrote of Paracelsus as 'the reformer par excellence' and of Harvey, by comparison as 'the author of a secondary discovery'.¹ Daremberg² appropriately commented:

Quoi! une découverte qui change la face de la science une découverte qui contient en germe tous les progrès futurs de la médecine, en un mot, la vérité, la réalité ne serait pas mille fois plus importante que des idées *a priori*, qui n'ont eu d'écho que dans quelques cerveaux prédisposés aux aberrations!

It would be impolite to attribute to members of the Paracelsus Society 'brains predisposed to aberrations', but it is not too much to ask that their future publications should be inspired by a rather less mediaeval scientific outlook. To imply, as de Telepnef does in an Addendum, that passages in the writings of Paracelsus have some prophetic relation to the atomic bomb is on a level with forecasts of the date of the Millennium derived from a study of the Old Testament or the architecture of the Great Pyramid.

N H J

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HISTORY OF A MENTAL HOSPITAL

The treatment of mental disorders (ancient and modern), by Richard Eager, commemorates the centenary of the Devon Mental Hospital, which was founded in 1845 as the Devon County Lunatic Asylum. The author of this little book was for thirty years a member of the hospital staff and its medical superintendent for fourteen, and is therefore well qualified to be its historian. The first part of the book is a brief history of the care and treatment of the insane from the earliest time. In referring to matters not strictly germane to psychiatric history the author sometimes falls into error, as when he states that Harvey first explained the circulation of the blood in 1610 and that he died in poverty. It is generally accepted that Harvey gave the first public exposition of his views in his Lumleian Lectures in 1616, and although his practice is said to have fallen off after the publication of his book on the circulation he never knew poverty: indeed he left more than £20 000 to his brother Eliab, apart from other bequests. The book contains many misprints and it is particularly disquieting in a history of

¹ Daremberg C. *Histoire des sciences médicales* vol. I p. 57 Paris 1870

mental disease to come upon such distortions of well known names as Kraepelin, Esquirol, Sherrington, and Wagner von Jaurigg.

In the second and third parts dealing with the history of his own hospital, with recent advances in psychiatry, and with the changing outlook on mental disease, the author is on surer ground. The story of a particular hospital, when fully told and well documented, is a source book of primary importance, and Dr Eager could have expanded that part of the book which tells the story of the Devon Mental Hospital and of the eminent physicians who have served it, to the advantage of his present readers and of future historians of psychiatry. [For price and other details, see BMB 921.]

W J B

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JOHN HUNTER

A bibliography of the works of John Hunter has recently been prepared by W. R. Le Fanu² librarian of the Royal College of Surgeons. The list records all editions of Hunter's works known to the compiler, it does not deal with his contributions to periodicals nor with his case histories and descriptions of specimens posthumously printed in the catalogues of the Hunterian Museum. The holdings of 25 of the most important medical libraries are recorded in each entry.

Mr Le Fanu points out that, besides their outstanding position in scientific literature Hunter's books are of bibliographic interest because several of them were published at Hunter's own house, 13 Castle Street, Leicester Square, London. He will welcome additions, corrections and records of library holdings in order that a detailed bibliography of Hunter may be prepared.

L T M

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DOMESTIC MEDICINE

Among the numerous works on household or popular medicine which have appeared since the *Regimen* of the School of Salerno first created a taste for this type of literature none has enjoyed a wider circulation than Buchan's *Domestic Medicine* which was first published in 1769. There have been many editions since then, and the book is in use even to this day as a family guide to health. William Buchan practised in Edinburgh and subsequently in London. There he died in 1805 and was buried in Westminster Abbey. Buchan's treatise gives an interesting picture of the times in which he lived. He states that one half of the children born in Great Britain die under twelve years of age and of smallpox, he writes: 'This disease is so general that few escape it at one time of life or another.'

Douglas Guthrie

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LIBRARY OF THE WELLCOME HISTORICAL MEDICAL MUSEUM

Dr E. Ashworth Underwood, the director of the Wellcome Historical Medical Museum, 183-193 Euston Road, London NW1, asks us to announce that a catalogue of the extensive library of the museum is being prepared, but that it will be some time before this work will be published. Meanwhile if any

² John Hunter: a list of his books. Compiled by W. R. Le Fanu. Printed for the Royal College of Surgeons of England at the University Press, Cambridge 1946. 31 pages.

person who is preparing a bibliography of the works of any writer in the field of medicine or the allied sciences, desires to include the location of known copies of the different works, Dr Underwood will be pleased to send him on request a list of the various works and separate editions of that writer which are in the library of the Wellcome Historical Medical Museum, and applications should be made to him in writing.

It is hoped to open the library for the use of students at an early date, and an announcement will be made to that effect, but meanwhile the above particulars will be supplied on request.

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SPANISH MEDICAL BIBLIOGRAPHY

El Indice Medico Progresivo (Barcelona) This new periodical provides a monthly index of all Spanish medical literature. The first number was published in April 1945 and comprises 4 sections: (i) A numbered and alphabetically arranged list of the periodicals covered, with date of publication of the issue indexed, (ii) a contents-list for the particular issue of each periodical, numbered as in (i), (iii) an alphabetical author-index including all joint authors and (iv) a subject-index. Number 12 of Vol. I will include a general index to the volume as a whole.

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SWISS MEDICAL BIBLIOGRAPHY

Bibliographia Medica Helvetica, 1, 1943 This is the first volume of a new bibliography of Swiss medical publications issued by the *Académie suisse des sciences médicales* in collaboration with the *Bibliothèque nationale suisse*. It is to appear once or twice a year and will include all the publications which have appeared in the course of a year, but it is also possible to obtain separate parts referring to a particular subject. The bibliography is arranged in classified order, according to the Universal Decimal Classification, with subject and author indexes. There is also a table of the relevant parts of the classification. This publication may be obtained from Benno Schwabe & Co., Basel, price 15 Swiss francs.

890

THE CAJAL INSTITUTE

Volume 36 (1944) of the collected works of the Instituto Cajal, *Trabajos del Instituto Cajal de Investigaciones Biológicas*, published annually under the auspices of the Consejo Superior de Investigaciones Científicas, has recently been received. It contains the following articles: "A Sheath enveloping the entire Ramifications of the Axon in the Motor Endings of Striated Muscles," by J. F. Tello, "Contributions to biological research. Part II. Animal Movements. Migrations," by Domingo Sánchez y Sánchez, "Experimental Poliomyelitis," by J. Sanz Ibáñez, "Contribution to the Study of the Cerebellar Neuroglia of the Lamb," by Demetrio Dimoff, "New Staining Technique specially applicable to Sections of Organs of the Nervous System," by Jose Luis Arteta Algibez, "Contribution to the Histopathology of Human Lathyrism," by C. Oliveras de la Riva, "The Mechanism of Excitation of the Chemoreceptors and Baroreceptors of the Glossopharyngeal Nerve, by means of a Reflex Arc between the Vago-afferent and Sympathetic Systems," by F. de Castro. The first and third articles are accompanied by summaries in English and German and the last by a summary in English.

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TROPICAL SCIENCE IN SWITZERLAND

In 1944 the Federal State Council for the creation of employment approved the foundation of a Swiss Tropical Institute in Basel which was to combine scientific research with the training of medical men, missionaries, zoologists, veterinary surgeons, pharmacists, manufacturers, engineers, etc., for work in tropical and subtropical countries. A tropical clinic was opened by the Institute in the Hilfsspital in Basel, with escaped prisoners of war and internees from Mediterranean regions, suffering from a form of malaria very prevalent in tropical countries, as its first patients. The teaching activities of the Institute include (a) a one-year general tropical course at the University covering all matters of which a European travelling to the tropics should be at least

roughly informed, but with a slightly differing syllabus for medical men, (b) a 3-year course for young people designed to give a thorough training for practical work in the tropics in one of three spheres, namely as a planter, sugar chemist or trader. Diplomas are awarded for both courses. Research on a number of malarial problems has already been begun, and it is thought that, with the post-war return of Swiss and other European business people, missionaries, etc., to Switzerland, the work of the clinic and the scope of the Institute's research will expand. A comprehensive research index of tropical literature is being compiled to facilitate this work. An expedition to West Africa was planned for the latter half of 1945, to make direct personal contacts with the authorities there, to visit tropical institutes and hospitals and collect information regarding the diseases treated and the researches pursued therein, and to arrange for the possible visits of Swiss scientists for further training.

With the foundation of the Tropical Institute there came into being a new periodical, the *Acta Tropica* which, as stated in the foreword to Volume 1, is intended to be "not merely the organ of the Tropical Institute but an independent international scientific review treating of the whole sphere of tropical science." The *Acta Tropica* is edited by Professors R. Geigy, A. Gigon, F. Speiser and R. Tschudi, "in collaboration with eminent Swiss and foreign specialists," and published by Verlag für Recht und Gesellschaft AG, Basel. One volume comprising four numbers of 96 pages each is issued annually at a cost of Fr. 30 (single numbers, Fr. 9). The bound copy of Volume 1 (1944) and the first three numbers of Volume 2 (1945) which have reached us amply confirm the stated aim of the *Acta*, which is to afford scope for the presentation of "scientific research pure and simple as well as that undertaken with a view to practical application" in the fields of anthropology and ethnography, natural history of the tropics, tropical agriculture, tropical medicine, and veterinary surgery and medicine in the tropics. A random sample of the titles of original articles will illustrate this Volume 1: The Influence of Polynesian Culture on New Caledonia and the Loyalty Islands, Tropical Medicine in the Middle East, India and the Dual Organisation, The Role of Parasitic Worms in the Tropics, The Yellow Populations of Africa, Progress in the Control of Typhus and Malaria. Volume 2: International Campaign against Foot and Mouth Disease, Plasmodium vivax and Feulgen's Nuclear Reaction, Phlebotomus in Switzerland, The Attitude of Catholic Missions to Native Art in the Tropics, The Secret Societies of West Africa, The Importance of the Medical Mission in Tropical Medicine. The articles appear in German, French or English, and are each accompanied by summaries in the other two languages. The international bibliography included in each number is classified according to the decimal system and should prove invaluable to students of tropical science. A book review section and a number of short scientific communications and reports under the heading "Miscellanea" complete the contents of this well-produced and beautifully illustrated journal.

M B IV

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ROYAL COLLEGE OF SURGEONS OF ENGLAND

General Annual Report of the Council, 1945

PUBLISHED BY THE COLLEGE, LINCOLN'S INN FIELDS LONDON W.C.2
26 pages - 15 x 14 cm.

This report, which covers the period August 1944 to July 1945, opens with an account of the visit to the College of H. M. Queen Mary on 13 July 1945.

The death at the age of 95 of Sir Buckston Browne has deprived the College of one of its greatest benefactors. His most important donation to the College was a gift of £100,000 for the establishment and endowment of the Buckston Browne Surgical Research Farm, Downe, Kent. The death of Sir William Girling Ball is also recorded in the report.

During the year 27 fellows and 571 members were admitted by examination. In the previous report¹ there was stated the intention of the Council to seek power to institute a final examination for Fellowship of the College adapted to the needs of ophthalmological candidates. This principle has now been extended to cover the case of otolaryngology. A higher quali-

fication in dental surgery has for long been considered, and Fellowship in Dental Surgery" has now been adopted as a suitable title

Sir William H Collins has donated a further £100,000 to the College, for the endowment of the department of anatomy and the institution of a chair of human and comparative anatomy Prof F Wood Jones has been appointed to this professorship

The College is to appoint from time to time research associates, with the object of providing for interested persons a suitable association with the College and its museum

In the department of pathology much thought is being given to reconstruction plans and to methods of arrangement and display in the future museum New specimens which have accumulated since 1941, over 600 in number, are being classified and prepared for museum purposes

The library office returned to the College during the year, and the reading room was reopened The return of the books from war-time evacuation is almost completed Accessions to the library include 100 volumes bequeathed by the late Sir Humphry Rolleston

The research work briefly noted in the report is more fully discussed in the scientific report²

During the year the College has maintained its policy of securing properties adjacent to its original buildings, plans for the rebuilding of which are under consideration

¹ [See BMB 606/101] ² [See BMB 893]

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ROYAL COLLEGE OF SURGEONS OF ENGLAND

Scientific Report for the Year 1944-1945

PUBLISHED BY THE COLLEGE, LINCOLN'S INN FIELDS LONDON W.C2
24 pages. 245 x 15 cm

Department of Pathology The newly-appointed Sir William H Collins professor of pathology, Dr R A Willis, commenced duties in April 1945 Much preparatory work has been performed in connection with the re-establishment of the museum The specimens surviving from the 1941 disaster, which had been dispersed in various centres, have now been returned to the College Accessions to the museum during the year number 230

Department of Anatomy During the earlier part of the year the main preoccupation of the anatomical museum staff continued to be the supervision of the dispersed specimens and the reception, registration and storage of incoming material Professor F Wood Jones was appointed to be first occupant of the Sir William H Collins chair of human and comparative anatomy Anatomical research during the session has included an investigation of the oesophageal vasculature Information on anatomical matters has been supplied to various enquirers 104 specimens were added to the anatomical museum during the year

Bernhard Baron Research Laboratories The work in these laboratories during the past 5 years is summarized Up to 1941 published work on trauma and repair showed traces of having been influenced by the investigations carried out between 1914-18 Thereafter the outlook was influenced by the mass of knowledge which accumulated on growth, metabolism and nutrition The work in these laboratories was therefore directed to studying the mechanisms involved in the maintenance of a constant blood volume It was found that, after haemorrhage, protein was being added to the extra-vascular fluid entering the circulation to restore the blood-volume The added protein came partly from the liver and partly from the muscles Later studies showed that plasma protein moved out of the circulation as rapidly as it entered after haemorrhage The problem of protein synthesis was attacked by indirect methods, using human patients In a normal individual the amount of protein destroyed each day is equal to the amount synthesized The net intake of protein can be estimated by determining the amount of protein in the food and subtracting from this the amount not absorbed in the gut From the urinary nitrogen content the amount of protein destroyed in the body each day can be estimated In 1943 it became possible to study in detail cases of infective hepatitis and allied hepatic diseases, thus providing data on the rate of protein synthesis The value of methionine in the prevention of hepatic necrosis was also observed It is

widely recognized that excessive protein loss is an inevitable consequence of trauma, and is thus a phenomenon common both to hepatic disease and to injury The necessity for the assimilation of adequate protein by patients became obvious There followed the use of pre digested proteins (hydrolysates), the employment of which speeded up wound healing in patients previously showing no progress on account of grossly inadequate protein intakes

As an outcome of various reports of the above work, the laboratories were asked to provide the nucleus of a laboratory team to study the results of the long food deprivation suffered by the people of western Holland and to report on the most effective treatment of the starvation state A report on this work is being submitted to the Medical Research Council

Dr F K Sanders has continued his work on peripheral nerve injuries

Details of papers published from the department's research laboratories during the year are included in the report (For review of previous report, see BMB 606/102)

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LONDON COUNTY COUNCIL

Interim Report of the Medical Officer of Health and School Medical Officer for the Year 1944

LONDON P S KING & STAPLES LTD 1945 50 Pages. 1s. 6d. [L0 075]

The interim report for the year 1944 of the County of London Medical Officer of Health and School Medical Officer (Sir Allen Daley) is the most comprehensive report of the series published since 1939, and for the first time since then it quotes birth- and death rates

The report states that London's population was down by 40% in 1944 compared with 1938, i.e. from 4,062,800 to 2,462,500, due mainly to evacuation and war service

In spite of the ordeal caused by V 1 and V 2 and the continued strain of war, the general health of Londoners remained on the whole satisfactory Tables analyzing civilian air-raid deaths in London show that 17,811 civilians were killed in the administrative county up to the end of 1944 There were 814,498 dwellings in London when the war started and of these 709,518 were affected by bombing about 70,000 being completely destroyed, 56,000 rendered uninhabitable and 66,000 seriously damaged 48,709 persons injured by bombing during the war were conveyed to hospitals or first-aid posts by the London Ambulance Service

During the war years there were about 660 bombing incidents at the London County Council's hospitals affecting all but 3 of the total number of 100 hospitals At no time, however, had urgent cases to be refused admission 17 of the hospitals had at various times to be evacuated and closed temporarily because of damage 257 patients were killed in air raids (out of a total of 1,200,000 patients admitted during the period) and 62 hospitals staff were killed 5,000 hospital beds were destroyed

About 8,700 patients were evacuated from the Council's hospitals during 1944 to hospitals in the province, and as part of the scheme, the Council on behalf of the Ministry of Health, administered 4 hospitals entirely new to the Council in North Wales, Yorkshire, Northumberland and Ayrshire

The maternity death rate in London is still decreasing, and in 1944 reached the record low level of 1.7 per 1,000 live births The maternity death rate has in fact fallen by more than half since 1934

There were less births (44,554) in 1944 than in 1943 (45,030) and mainly on account of air raids, more deaths (41,077) than in 1943 (39,322) The birth rate steadily increased during the war years, although the marriage rate has decreased since 1941

The infant mortality rate, 51 per 1,000 live births, was the same as in 1943

The report makes an interesting comparison between the vital statistics of London and New York showing that the London birth rate is at present increasing while the New York birth-rate has fallen since 1943 that the London death-rate is higher than the New York death-rate that the infant mortality rate for London is substantially higher than that for New York that the maternal mortality rate is about the same for both cities that the accident death rate, including street accidents is about the same in both cities, that mortality from pulmonary tuber-

culosis in London is about twice, while that from other forms of tuberculosis is between three and four times, that in New York, and that the death-rate from influenza is much higher in London than in New York

The nutritional condition of the great majority of London school children still continues to be satisfactory and is, in fact, better than in 1938, a great tribute to the work of the Ministry of Food. Following the evacuation of children from London in 1944 there was no recurrence of the complaints about their condition which were received in 1939. On the contrary, many letters referred to the surprisingly good health and cleanliness of the children, especially in view of the state of London and the shelter life which then prevailed.

4,065 children were immunized against diphtheria during 1944 by the medical staff of the London County Council, making a total of 65,199 children immunized since 1940, in addition to those immunized by the medical staffs of the Metropolitan Borough Councils. By July 1944 about 68% of London elementary-school children had been immunized.

There was a decrease in the number of new notifications of tuberculosis (5,729 in 1944 compared with 5,848 in 1943) and also in the number of deaths (2,310, or 0.94 per 1,000 population, compared with 2,460). Miniature mass radiography examination of various sections of the public, for the early diagnosis of the disease, was continued during 1944. 46,671 miniature films were taken and 1,795 large films (about 3.85% of miniatures) were taken in those cases where the miniature film disclosed any significant abnormality. Particulars are given (page 26) of the classification of the large films. For every 10,000 persons who volunteer to have their chests x-rayed, 24 are found to be in need of sanatorium treatment. Over £120,000 was paid during 1944 in allowances to patients undergoing prescribed treatment.

There were 206 deaths from influenza in 1944 compared with 726 in 1943, when there was an epidemic in January of that year. Scarlet fever was appreciably less prevalent in 1944 than in 1943 and there were 7 deaths compared with 11 in the previous year. There were 2 notifications of smallpox in 1944.

There were 178,433 admissions during 1944 to the Council's public health hospitals. 13,050 births (12,612 live births) took place in the Council's general hospitals and, in addition, 5,924 confinements at home were attended by the Council's own midwives. (There were about 21,000 births a year in the Council's hospitals before the war.)

With regard to the Council's mental health services, there was a continued fall in the number of mental patients. During 1944 about 29,500 patients passed through the emergency (general) hospitals attached to the mental health services.

The report pays a tribute to the staff of the Council's health services who, despite continued, and in many respects more acute, war-time difficulties, kept the services running efficiently.

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A NEW UNIT FOR RESEARCH INTO THE COMMON COLD

It is announced that a "Common Cold Research Unit" has been established by the Medical Research Council and Ministry of Health, and that the work of the unit will have started by July, 1946. The Ministry of Health and the Medical Research Council point out that the problem of the common cold is a particularly complex one, made more difficult because, apart from chimpanzees, which are unsatisfactory for experimental purposes, it has not yet proved possible to study it in animals.

Progress towards the discovery of effective means of preventing a number of other diseases has not been made until some way of observing the disease in animals became available. For example, an effective vaccine against yellow fever became possible only when rhesus monkeys, and later mice, were found to be susceptible to the virus of the disease. Similarly, not until it was discovered that ferrets were susceptible to influenza virus was any progress made with the study of influenza. Therefore, the first objective of the present investigations into the common cold is to find a susceptible animal or, better still, some other laboratory technique which will permit a scientific approach to the problem.

As a check on their laboratory studies, workers at the National Institute of Medical Research will, at least for the time being, require to test on human volunteers the cold-producing activities of materials they are studying. Volunteers will first be isolated until it is certain that they are free from infection. Then, after a few days' quarantine, their noses will be sprayed with material to see whether or not it contains a virus. While these observations are being made—for a period of 10-14 days in all—the volunteers will be out of contact with the outside world and each other except that, to obviate the boredom of solitary confinement, they will normally live together in pairs. Isolation will not involve complete loss of freedom, for the volunteers will be allowed to move about the countryside around the hospital, provided they avoid all human contacts, and will live in restful and comfortable holiday conditions. Volunteers are already being recruited from among university students. If more are needed later, an appeal will be made through suitable organizations. Volunteers must be carefully selected, because special qualities are needed and an exact discipline must be maintained. For this reason the Medical Research Council is selecting its own recruits, and applications from the general public cannot be entertained.

Progress towards the solution of the many problems which face the medical scientists undertaking this research work is likely to be slow, and it would be unwise to expect any spectacular advance, at any rate in the near future.

* * *

More about early Ether Inhalers

Since we published, in our last number, a considerable amount of material on the history of anaesthesia, including the development of inhalers¹, we have received an interesting paper on "Ether inhalers in early use", by Dr William W Ford², of Baltimore.

Dr Ford reproduces figures of the following inhalers: Morton (USA, 1846), Morton & Gould (USA, 1847), Squire (England, 1847), Gilbertson (England, 1847), Tracy (England, 1847), Smee's Portable³ (England, 1847), Salt (England, 1847), Gallard (country of origin not stated, 1847), Snow⁴ (England, 1847), Liler (France, no date), and Charriere (France, 1847). Several other inhalers are referred to in the text. An interesting point made by Dr Ford is that trials of ether in France preceded those in England by a few days. On 15 December 1846, an unsuccessful demonstration of ether anaesthesia took place at the Hôpital Saint-Louis, Paris.

¹ See especially *BMB* 827, 829, 830.

² *New England Journal of Medicine*, 1946, 234: 713-726.

³ This is a different model to that figured in *BMB* 830.

⁴ A different apparatus to that figured in *BMB* 827, 829.

The Library

Publications discussed or listed in this section may be borrowed by inquirers resident in the United Kingdom on application to the Editor

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A FRENCH WORK ON VIRUS DISEASE

Professor C. Levaditu's latest book (*Précis de virologie médicale*, 250 pages, 142 illustrations, Paris, Masson, 1945) is designed to give the physician and student some insight into current work on the virus diseases of man. It is well printed and very freely illustrated, though, as is still the way with the French, the histological aspects are portrayed in drawings rather than in photographs. The reader will obtain a useful survey, especially of the work of Levaditu's own school, the allotting of pages to the various viruses is rather closely related to the attention they have received in the author's own laboratory. There is a freely illustrated chapter on virus techniques.

At this time many Continental workers are visiting Britain and the United States to acquaint themselves with recent developments in research from which they have been cut off since 1940, 1945 seems accordingly a singularly unfortunate moment for a Continental worker to have attempted to produce a review of such a rapidly-moving subject as virology. One sees, for instance, no mention of Hirst's haemagglutinin test in influenza, described in 1941 and now the most generally useful laboratory method for workers on that disease. Of references to authors there are many, but these are all, whether by design or oversight, left "in the air." We read "Levaditu (1925)" or "Blanc (1921)," but look in vain for a bibliography in which to discover where to pursue our studies of these authors' writings.

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RADIOBIOLOGY IN FRANCE

In a contribution¹ to the "Collection des Actualités Radiobiologiques" published under the general direction of MM. Dognon and Biancani, Dr J. Lavedan has given a brief summary of the action of penetrating radiations on the cells of normal tissues. The book is in two parts. In the first (48 pages) the author discusses the relative importance of the effect on nucleus and cytoplasm (chapter 1), the changes in radiosensitivity associated with various biological functions of the cell such as mitosis, segmentation, metabolism and so on (chapter 2), and then "inverting the problem" he describes the action of radiation on particular activities of the cell, e.g. mobility, reproduction, respiration, permeability, etc (chapter 3). Here he quotes Lacassagne's description of the dissociation of cell functions produced by radiation as a "physiological micro-dissection" peculiar to this agent.

The second part of the book (57 pages) deals with the physical factors of radiation and includes some consideration of the mechanism of the action of radiation (chapters 1 and 4), the significance of wavelength and the time-factor (chapter 2), radiation induced mutations (chapter 3), and a summary of conclusions (chapter 5). This is followed by a short addendum of six pages on recent ideas about the mechanism of the action of radiation which might more conveniently, for the reader at least, have been included in earlier sections of the book.

The bibliography is disappointing. Nearly 300 names are mentioned in the text, but only 96 references, comprising 65 names, are quoted in full. Instead the reader is referred to Lamarque's recent book² where, he is told, he will find a very complete literature.

F G S

¹ L'action des radiations sur la cellule normale. Paris 1945. 128 pages.

² Lamarque P. Les bases physiques et biologiques de la roentgentherapie. Paris 1942.

898

YELLOW FEVER

In 1932 members of the Rockefeller Foundation working on yellow fever in Brazil introduced the viscerotome to obtain specimens of liver for diagnosis of fatal illnesses. This method has proved to be of inestimable value in studying the epidemiology of yellow fever, especially the jungle type.

In 1935 the French Government commenced similar studies in French West and Equatorial Africa in order to define the endemic areas and detect any spread of the disease in an unrecognized form. J. Bablet has examined several hundred specimens of liver from suspected cases collected in these regions from 1935-43. As a result of these studies, and in order to aid the physicians and pathologists encountering cases suspected to be yellow fever, he has (*La fièvre jaune*, Paris, 1945, 69 pages) summarized briefly the clinical picture and differential diagnosis, the laboratory tests used in diagnosis, the best methods of preparing tissues for histological examination and the specific pathological lesions and differential diagnosis of them.

Bablet advocates the use of the viscerotome in all patients, febrile or non febrile, jaundiced or not, who die in less than 11 days from the onset of their illness. Pieces of liver and kidney where possible are fixed in 10% formalin and sent to the nearest pathological laboratory. The advantage of the viscerotomy service is that personnel with no knowledge of medicine can collect the desired specimens.

As a result of the examination of his own material and the large collection of specimens in Rio de Janeiro, Bablet considers that there is a histological picture which is specific for yellow fever. The lesions, which are the same as those previously described from West Africa and South America, consist of generalized fatty degeneration and a coagulation hyaline necrosis (Councilman lesion) and chromatolysis of the nuclei of the parenchymal cells chiefly in the mid zone of the lobule. Once more attention is drawn to the frequent occurrence of chronic hepatitis among the African natives and Syrian traders who have lived in the country many years. This lesion frequently influences the usual clinical picture of yellow fever, resulting in death in 3 to 4 days with little or no fever. The previous histological changes mask those of yellow fever. Councilman lesions are rare and there are extensive recent haemorrhages.

The author stresses the usefulness of the viscerotome in providing information of the incidence of other lesions of the liver in the courses of the yellow fever studies and also as a routine method for studying hepatic lesions in disease of other tropical countries.

F O MacCallum

899

FRENCH VIEWS ON THE PROLAPSED INTERVERTEBRAL DISC

In *Sciaticques et lombalgies par hernie postérieure des disques intervertébraux* Prof. D. Petit-Dutailis and Dr S. De Sèze present the first French monograph on the surgical aspect of sciatica. It is based on 50 of their own cases, and will certainly be of great value to the French-speaking medical world.

From the clinical point of view they are in almost complete agreement with the Anglo-American authors as regards history, symptoms and signs. Myelography is employed in every case, but in recalcitrant and chronically incapacitating cases of sciatica the operation is indicated anyway, as the root compression may be due to "funiculus with root oedema, isolated hypertrophy of the ligamentum flavum, arachnoiditis or even gross spondylitis." Fully aware of the risks of lipiodol, the authors advocate its removal by making a small incision into the theca at the end of the operation, in order to prevent what they call "huilomes" ('oleomata').

The operation is done under local and intra-arachnoid anaesthesia, occasionally supplemented by pentothal. They favour a large exposure, including bilateral ablation of two laminae, and of the articular processes. Only large protruding fragments are removed. In recent cases they have practised posterior rhizotomy. This is advocated in spite of the claim that no true relapses were observed among 50 cases of which nearly all returned to their work. Minor complaints such as

backache, are admitted to occur, but only for short periods. The indications for osseous grafts are considered to be practically non-existent.

Conservative treatment should always be tried first, except in cases of paralysis and cauda equina lesions. If after adequate bed-rest and the other usual measures, there is no improvement, a surgical belt is often employed, in cases of marked spinal deformity this is preceded by the application of a plaster jacket to be worn for one or two weeks.

A well documented and illustrated discussion of the possible aetiology, anatomy and pathology of the lesion is a great asset to the book, as are the numerous radiograms and operative sketches. The lucid presentation should acquaint many with a sound way of dealing with an incapacitating malady, for the understanding and treatment of which these two authors have done outstanding pioneer work in France.

F Schiller

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BIOENERGETICS

Samuel Brody's *Bioenergetics and growth*¹ is a monumental work and will become a classic. In just over a thousand pages the author presents succinctly and yet comprehensively an integration of the results of the researches of the Agricultural Chemistry Division of Missouri Agricultural Experiment Station concerning the quantitative energetic efficiencies of agricultural processes such as those concerned in the maintenance and in the production of meat, milk, eggs and muscular work, along with the principle of diminishing returns and its relation to planes of nutrition. In addition, consideration is given to the relation of the speed with which these transformations occur to the efficiency of the process, and to the influence of the size of the producing animal on the efficiency and profit of the productive enterprise. The book is also concerned with nitrogen metabolism, with growth, development and aging, and with the catalysis of these processes.

The one hundred and fifty-fold increase of the human population in the past 100 years in the USA is held to be a direct consequence of the progress in agricultural production.

Here we have both scientist and philosopher, for the author has felt the need for a unifying principle when writing this immense work which would interrelate all the various components. The concept of physiological regulation as enunciated by Sherrington when he stated that "the organism acts as though it desired to maintain itself", or, more recently, by Cannon when he coined the term "homeostasis", comes nearest to meeting the need for such a generalizing principle. The philosophic note in which this remarkable book ends is that the future trends of human behaviour and social phenomena, although unpredictable and the despair of the social scientist, are at the same time the hope of humanity, for man is given an opportunity to mould his destiny that is not permitted to other species that are subject to more determinate, orderly laws.

D P Cuthbertson

901

TRYPANOSOMIASIS. A NEW MONOGRAPH

In the abstracts which appear month by month in the *Tropical Diseases Bulletin* and the *Bulletin of Hygiene*, and in the *Bulletin of War Medicine* during the war, the Bureau of Hygiene and Tropical Diseases records the current literature on subjects coming within its fields of interest. From time to time the Bureau has been asked for information on some particular branch of medical work to be collected together in the form of a monograph for the greater convenience of persons concerned with a special problem. This is a service, which, because of its day-to-day abstracting organization, the Bureau is favourably placed to perform. Such a monograph has recently been

¹ *Bioenergetics and growth with special reference to the efficiency complex in domestic animals*, by Samuel Brody. New York, Reinhold Publishing Company 1945. 1023 pages. \$8.50.

compiled for the Tsetse Fly and Trypanosomiasis Committee appointed by the Secretary of State for the Colonies, and though designed to meet a particular need it is thought that its publication may prove useful to a wider public. "A survey of recent work on trypanosomiasis and tsetse flies" is therefore now published as *Bureau of Hygiene and Tropical Diseases Review Monograph No 1*, and provides a brief statement of the work done, and some of the opinions expressed, by those who have worked at the different problems concerned with trypanosomiasis since 1931. The monograph is obtainable from the Bureau, Keppel Street, London, W C 1, price 7s 6d [£0.375]. 81 pages, 1946.

902

A RUSSIAN SURGICAL CLASSIC

N Pirogov. *The foundations of general war surgery*. 2 vols. Moscow, 1941 [In Russian].

Seventy-five years ago, Pirogov published his classic work on "The foundations of general war surgery", basing his studies on his experiences in the Crimean War and the Caucasian Expedition. In 1941 these two historic volumes were republished in a new edition by Prof N Burdenko. Burdenko states in his foreword that this work is a most valuable contribution to war surgery, although it was written so many years ago, and that it is still a fundamental guide to surgeons all over the world. Pirogov's voluminous treatise deals with the study of traumata and of the general reaction of the body to trauma, with the local reactions to trauma, with the study of wounds, their course and complications, further, with the study of gun-shot wounds, complicated and uncomplicated, with the treatment of wounds of soft tissues, infected and not infected, with the study of plaster bandages and, finally, with wounds of cavities. If one remembers that 75 years ago all these subjects were hardly investigated and described and also remembers the primitive conditions available in those days, one can judge what a tremendous task Pirogov undertook and how magnificently he achieved his object.

H W Swann

903

SOME RUSSIAN SURGICAL WORKS PUBLISHED DURING THE WAR

C L Schneider. *Transplantation of skin by the sieve method*. Novosibirsk, 1944 [In Russian].

The author strongly advocates the method of skin transplantation described by the American surgeons Dragstedt and Wilson in 1937. The method consists of a transplantation of the whole thickness of the skin (without the fatty layer), which is perforated in many places to resemble a sieve. The author recommends this method even in emergency operations and also describes many other operations, where this method has been most successful. The author also devotes a special study of the way the defect should be prepared for the transplantation. The book is based on personal experience during a period of 6 years and describes not only the successful cases, but also the failures.

V A Negovsky. *An experiment in treating conditions of agony and clinical death at the front line*. Moscow, 1943 [In Russian].

This book is a sequel to the author's previous study of the restoration of life functions of the body which is in a state of agony or clinical death. The experiment was carried out at the front line during a period of four months. In all 51 cases of agony and clinical death were treated and in 12 cases there was a complete cure. In 37 cases there was only a transient effect and the patients died later on account of the severity of their wounds. Only 2 cases did not respond to any measures of every resuscitation. The author gives a detailed account of every case. He emphasizes that the first three minutes, in which a resuscitation can be attempted, are the most vital. The thoroughness and efficiency of the preliminary preparation is most essential.

V A Negovsky. *The restoration of life functions of the body which is in a state of agony or clinical death*. Moscow, 1943 [In Russian].

Biological or irreversible death is usually preceded by a period of clinical death, which is diagnosed from the moment of

cessation of the heart action and respiration. The aim of this book is a study of certain aspects of the pathology and physiology of the dying process and the subsequent restoration of the life functions of the body. There is a detailed study of the functions of respiration and circulation of the blood, of the metabolism and the resistance of the central nervous system to anaemia. The experiments were made on animals, which were subjected to complete loss of blood. There are also some experiments on the resuscitation of asphyxiated new born babies.

J. A. Kopylov *Amputations and the amputated*. Leningrad 1943 [In Russian]

This is a short, but rather detailed, account on amputations. The author first gives a historical survey and describes what the imperfections of amputations were in the past and then proceeds to outline how the optimum results can be obtained, and how amputations should be done at the front so as to facilitate the work of the surgeons in the rear. One chapter deals with the transplantation of the skin to cover up defects and another with the problem of how to shorten the period of hospitalization of the amputated.

E. Salkindson *Physiotherapy in war injuries*. Leningrad 1943 [In Russian]

In the general part of the book the author deals with the physiotherapy which can be provided near the front line and at the different stages of evacuation of wounded and also with the equipment which is necessary for that purpose. The special part of the book gives a review of a large number of injuries where physiotherapy is essential. It deals particularly with the use of physiotherapy in gunshot wounds of all kinds, gas gangrene, injuries to bones and joints, congelations and burns, and finally to injuries of the nervous system. The book also gives a complete list of all necessary forms for statistical purposes.

H. W. Swann

BOOKS FROM FRANCE

904

B. Fey & P. Truchot *L'urographie Intra-Veineuse*. Masson et Cie. Paris 1944. 209 pages.

This is a valuable treatise on the subject of excretion urography. The greater part of it consists of reproductions of x-rays illustrating normal and diseased conditions of the urinary tract each with an adjoining note which explains the points to which attention is directed. In the text a full account is given of the origin of this method of investigation, the technique to be adopted, possible accidents which may follow imperfections of technique and a discussion upon what may be expected to be derived from the intravenous urography. There are chapters on each of the important renal diseases and in these the special uses of the method are discussed. It is rightly pointed out that of all methods of urological investigation this is the least harmful, the least unpleasant, and the most illuminating. Professor Fey in a foreword remarks that the precise interpretation of the radiographs requires an expert with specialized knowledge. Urologists everywhere will agree with him for they know full well that first-class x-rays are essential and that in many instances a diagnosis can only be established by consultation between the urologist and the radiologist concerned. The authors have employed as an injection 50 cm³ of tenebryl of 30% strength, a table is given of suitable doses for children. A chapter is devoted to the method as a test of renal function and its great value in this respect is emphasized. Attention is frequently drawn to the values of the test of von Lichtenberg, which is a comparison of the relative shadow densities of the two sides, and the test of Ravasin which studies specially the time of appearance of the drug in each kidney, the earlier shadow indicating the better kidney. These two tests are usually but not always found to be in agreement and judgment upon the results of them must be nicely balanced. Little space is given to the bladder shadows produced in excretion urography and whilst it is certain that cystoscopy is a more accurate method something further might have been said as to the value of this for it not infrequently shows the need of further investigations which might otherwise be regarded

as superfluous. English readers will find the *table de matieres* inadequate; it is what they will call merely a list of 'contents'. A true index of subjects, methods, diseases and names would add to the value of the book.

It is notable that this volume was produced in Paris in 1944. The type is excellent, the paper of good, though not the finest, quality, and suitable for the reproduction of radiographs. English writers who have experienced great difficulties in getting their books published during the war will be amazed that this was possible during the German occupation. Fortunately it has been done and a valuable book for study and reference has resulted.

Edwin Sidi *Les accidents cutanés des teintures capillaires. La sensibilité à la para-phénylènediamine*. Flammarion Paris (7) 1945. 152 pages. 21 figures. 195 francs.

The author has had the opportunity of examining nearly 300 cases of skin affections which could be proved to be due to hair dyes, in almost every instance the dye used had paraphenylenediamine as its base. The book is divided into five parts: I General—Chemical and biological properties of dyes derived from aniline, II Clinical and therapeutic study, III The problem of pathogenesis and the tests, IV Prophylaxis, V Medico-legal aspects. The author lays particular emphasis on the importance of methods of protection and the advice to be given to hairdressers and others whose livelihoods are affected by their sensitivity to such dyes. There is a bibliography of some 50 references and the book is well illustrated.

Pierre Mollaret & Ivan Bertrand *L'Hypertonie de décébration chez l'homme*. Masson Paris, 1945.

This monograph by two members of the staff of the Salpêtrière was inspired by the case of a man with so-called decerebrate hypertonia following encephalitis, and lasting 17 years. A detailed study of the case forms the central part of the book, the other two sections comprising an exhaustive examination of previous work on this subject by physiologists and clinicians. A comprehensive bibliography is appended.

Rémy Adrien Delauney *La pénicilline*. Presses Documentaires Paris 1945. Second edition.

The author sets out to collect, and present in a small volume accessible to any educated reader, the essential facts in our present knowledge of penicillin. After a brief historical note, he describes the culture of penicillium, the extraction, constitution and experimental and therapeutic action of penicillin in some detail, concluding with a chapter on 'Other bactericidal substances of fungoid or bacterial origin'. There is a bibliography of 115 references.

L. Tavernier & Ch. Godinot *Traitement chirurgical de l'arthrite sèche de la hanche suivi de travaux de la Clinique Orthopédique de la Faculté de Lyon*. Masson, Paris 1945.

This work, by the professor of paediatric and orthopaedic surgery at Lyons and his co-workers, is based on the authors' long clinical experience. The first and main part deals with the surgical treatment of rheumatoid arthritis of the hip. After describing the condition in detail, the authors consider the various types of operation they have used in the course of 25 years, ending with a chapter on the indications for the different operations. This part is completed by a list of 108 case histories. The second part deals more briefly with the surgical treatment of rheumatoid arthritis of other joints while the third part is a collection of articles describing the authors' work on orthopaedic surgery during the last few years. Some of these have not been published before though most of them have already appeared in journals. The book is well illustrated but has no index, and the only bibliography is a short one attached to one of the articles in the third part.

Hémoptyses non tuberculeuses et hémoptyses sur causes. (G. Doin & Cie. Paris 1945) by Jacques Lecomte.

The author has made a systematic study of 65 cases of non-tuberculous haemoptysis and here presents the results of diagnosis by means of bronchoscopy and lipiodol bronchography. The first two chapters comprise preliminary discussions of the diagnostic problems of haemoptysis and the relative value of these two methods of diagnosis, the subsequent chapters (IV-IX) are devoted to a detailed and classified study of results in

the author's own cases. The causes of 55 of these were revealed by bronchoscopy, of the remaining 10, 5 were identified by means of lipiodol bronchography, 5 alone being still unidentified after both methods had been used.

905

BOOKS IN SPANISH

Oxigenoterapia (Manuel Marín, Barcelona, 1945), by J. Chabas, editor of the *Revista de Higiene y de Tuberculosis*, will, writes Dr. Marañón in his foreword, do much to increase the prestige of this valuable therapeutic auxiliary, which has not hitherto received all the recognition it deserves. Dr. Chabas devotes 30 pages of his book (Parts 1 and 2) to a discussion of the theory of oxygen therapy, covering such problems as anoxia in respiratory and circulatory pathology, basal metabolism and the pathogenesis and diagnosis of endocrine disorders, acid-base equilibrium and blood pH, and many others. The third part gives a preliminary description of the various types of apparatus, the technique of treatment, the possible accidents and risks which have to be considered and the effects of hyper- and hypoxigenation. The fourth and main part deals with oxygen therapy in diseases of the respiratory system, the circulatory and digestive apparatus, and the nervous system, in gynaecology and obstetrics, in infectious diseases, and in surgery, and a final chapter considers its possibilities in a miscellaneous selection of diseases from cancer to sprue. Brief sections on ozone and carbon dioxide therapy are appended.

Plantas medicinales aromáticas o venenosas de Cuba (Habana, 1945), by Dr. Juan Tomás Roig y Mesa, chief of the chemistry department of the Agricultural Experiment Station at Santiago de las Vegas, is one of a series of technical publications of the Cuban Ministry of Agriculture. As stated in the foreword, this 2-volume monograph seeks to give as complete and exact an account as possible of the medicinal and poisonous plants of Cuba, to provide students of botany, pharmacy, medicine, agriculture and veterinary science with a work of reference, to stimulate Cuban scientists to further study of the local medical and toxicological flora, and finally to encourage the cultivation and development of indigenous and acclimatized medicinal plants. A preliminary grouping of plants, according to their uses, precedes the main body of the work, which gives details regarding synonyms, habitat and distribution, botanical descriptions, therapeutic properties and references for further reading, for over 1,500 plants. Three separate indexes (a) of common Cuban names, (b) of scientific names and (c) of names in common use in other American countries, complete this comprehensive study.

La penicilina y sus aplicaciones en oftalmología (Mexico, 1945), by Antonio Ros, represents the content of a lecture delivered by the author at a meeting of the Sociedad de Médicos of the Hospital Español, Mexico, and "sent to the printers without further corrections or additions." Brief introductory sections on the clinical importance of penicillin and the history of its discovery are followed by a review of its properties, clinical value, effects, toxicity and dosage, and finally by a discussion of its applications in ophthalmology—particularly as a prophylactic medium in the surgery of the eye—in relation to the author's own practical experience. Illustrative case-histories and a bibliography complete this concise account of the new drug.

906

PUBLICATIONS FROM BARCELONA ON THE PROBLEM OF THE ABANDONED AND DELINQUENT CHILD

The following have been received from Barcelona.

- Manich, F. & Córdoba, J. *Higiene social de la infancia*, Barcelona, 1943.
 Albó Martí, R. *Cuatro colonias agrícolas para menores moralmente abandonados*, Barcelona, 1942.
 Albó Martí, R. *El tribunal tutelar de menores de Barcelona en el año 1943*, Barcelona, 1944.

- Albó Martí, R. *El tribunal tutelar de menores de Barcelona en los años 1939 y 1940*, Barcelona.
 Albó Martí, R. *Estadística de los factores influyentes en el extravío de los menores ingresados en 1944*, Barcelona, 1945.
Boletín de Actividades de la Junta Provincial de Protección de Menores, Barcelona, 1945.

907

JOURNALS RECEIVED

Vol. 1, No. 1 of the *Journal of the Palestine Arab Medical Association*, "the first Arab medical periodical to be published in Palestine," appeared in November 1945. In addition to the Arabic section it contains five original articles, a "General Medical News" section and two brief reports: "Comparison of various types of local treatment in a controlled series of experimental burns in human volunteers" and "Intradermal use of convalescent serum" in the English language. As stated in the foreword, this Journal is designed to meet "a long felt need among Arab medical men for a local periodical in which can be recorded for study and reference the results of their research and experience, especially in endemic and other diseases peculiar to the country and to the Mediterranean basin."

Clínica Tisiológica (Rio de Janeiro) Vol. 1 (1944), which has just reached us, reports (in nine signed articles) the scientific activities of the clinical staff of the Hospital Miguel Pereira, which has recently developed from a hospital for the surgery of chest disease into a centre for the diagnosis and active treatment of pulmonary tuberculosis.

Ciencia e Investigación (Buenos Aires) The twelve numbers comprising vol. 1 (1945) of this monthly journal, published under the auspices of the Asociación Argentina para el Progreso de las Ciencias, have recently been received. The journal is intended to give a general account of present-day developments in the exact sciences, not to publish highly specialized articles in any particular field. Each number contains three or four signed articles, a book review section, a number of brief notes on recent researches in various parts of the world, and information on the activities of the Asociación. This is a most stimulating and attractively produced scientific monthly, which should be of interest to workers in all branches of science.

Cirugía del Aparato Locomotor (Madrid) The first number of Vol. II (January 1945), which has just reached us, contains 6 signed articles and short sections devoted to reviews of Spanish medical books and to abstracts of articles from foreign journals respectively. The journal is published quarterly.

Archivos de la Sociedad Oftalmológica Hispano-Americana (Madrid) Vol. 5, No. 10 (October 1945) of this monthly journal published under the auspices of the Consejo Superior de Investigaciones Científicas, has recently been received. In addition to 8 original papers, 2 clinical notes and summaries of a series of 5 lectures on the vascular pathology of the retina, abstracts of papers read at the various sessions of the Society's twenty-third congress are given. A final section comprises abstracts from foreign literature.

Anales Españoles de Odontostomatología (Madrid) This monthly journal is now in its fifth year of publication. The December 1945 number which has just been received contains 3 original and 2 review articles and brief bibliographical and abstracting sections.

Prótesis (Buenos Aires) This quarterly journal published by the Sociedad Odontológica Argentina de Prótesis is now in its ninth year of publication and is excellently produced and illustrated. No. 28 (March, 1945), which has just been received, contains 7 original articles and short abstracting and bibliographical sections.

Publicaciones del Instituto Antituberculoso 'Francisco Moragas' (Barcelona) Volume VI (1945) comprises two sections the first reproduces the text of a course of 6 lectures, given in April 1944, under the heading "Physiology of the Neuromuscular System of the Lung", the introductory lecture, by C. Zalabarder, bears the title of the heading, while the fifth and sixth lectures by the same author deal with "Atelectasis" and "The Lessons of Thoracoscopy and Monaldi's Method" respectively. The remaining lectures of the course are "Respiratory Physiomechanics and its Value in the Pathology and Therapeutics of Pulmonary Tuberculosis", by J. Argemí Lloberas, "Clinical Disagreement with Mechanical Ideas", by E. Alegret, and "Anatomy and Physiopathology of the Pulmonary Regions", by I. Blajot Pena. In the second section H. Sanjuán Nadal gives an account of his researches on the biology of Koch's bacillus under the title of "Some Problems in the Bacteriology of Tuberculosis", illustrated by a number of photomicrographs, and accompanied by a bibliography.

Revista Ibérica de Parasitología (Granada) This quarterly publication from the Instituto Nacional de Parasitología of the University of Granada is sponsored by the Consejo Superior de Investigaciones Científicas. The January-April 1945 issue (Vol. V, Nos. 1 and 2), which has recently been received, contains a lengthy thesis on bowel obstructions caused by *Ascaris*, an article on the susceptibility of domestic and wild animals to *Spirochaeta hispanica*, and Part II, Chapter III of a compendium of Iberian helminthology, the heading of which is 'Familia Taeniidae Ludwig 1886'.

908

OTHER BOOKS RECEIVED

- Bariéty, M. & Brocard, H. *Les septicémies à staphylocoques* 252 pages Paris, J-B Baillière, 1945
 Cambessédès, H. & Boyer, J. *Hygiène des institutions de plein air* 172 pages Paris, J-B Baillière, 1946
 Chauchard, P. *Le système nerveux et ses inconnues* 126 pages Paris, Presses Universitaires de France, 1944
 Courrier, R. *Endocrinologie de la gestation* 399 pages Paris, Masson, 1945
 Duhamel, G. *Régimes alimentaires usuels de l'adulte* 169 pages Paris, J-B Baillière, Paris, 1946

- Gouin, J. *La leucocyto reaction Elément de diagnostic et de thérapeutique Applications en syphiligraphie, dermatologie et médecine générale* 252 pages Paris, Masson, 1945
 Guillaum, G. Bertrand, I. & Gruner, J. *Les gliomes infiltrés du tronc cérébral* 286 pages Paris, Masson, 1945
 Huriez, C., Dumont, R., Patoir, G. & Leborgne, J. *Les gonococcies sulfamido-résistantes* 61 pages Paris, Masson, 1945
 Kolff, W. J. *De kunstmatige nier* 200 pages Leiden, Kok, 1946
 Mallet-Guy, P. & Maillet, P. *Hypoglycémies spontanées Le traitement chirurgical de l'hyperinsulinisme* 102 pages Paris, Masson, 1944
 May, R. M. *La formation du système nerveux* 300 pages Paris, Gallimard, 1945
 Milan, G. *La syphilis occulte* 181 pages Paris, J-B Baillière, 1946
 Monnier, J. *La pénicilline à la portée du praticien et son emploi dans le traitement des maladies vénériennes Pénicilline et syphilis Pénicilline et gonococcie* 148 pages Paris, J-B Baillière, Paris, 1946
 Peña, A. y E. *La resección transuretral de la próstata* 150 pages Madrid, Ediciones Morata, 1944
 Policard, A. & Galy, P. *Les bronches Structures et mécanismes à l'état normal et pathologique* 191 pages Paris, Masson, 1945
 Sanz Ibáñez, J. *Poliomielitis experimental* 127 pages Madrid, Consejo Superior de Investigaciones Científicas, 1944
 Sidi, E. *Les accidents cutanés des teintures capillaires La sensibilité à la paraphénylènediamine* 151 pages Paris, Editions Médicales Flammarion, 1945
 Suarez, F. G. *La carditis reumatica (carditis nodular estrepto-focal recidivante) Errores de la doctrina clásica Tratamiento profilactico de las recidivas* 235 pages Madrid, Ediciones de los Estudiantes Espanoles, 1945
 Urburu, J. V. *Oclusión intestinal Tratamiento medico mediante el sondeo aspirador y medidas asociadas Con un apéndice sobre la aspiración en cirugía gástrica* 377 pages Buenos Aires, El Ateneo, 1945
 Varela Fuentes, B., Recarte, P. P. & Graña, A. *Alergia en la practica clínica* 974 pages Buenos Aires, Espasa Calpe Argentina-S.A., 1946

Films

909

Personnel Selection in the British Army in 1944: Recruits

made by Shell Film Unit, 1945, in co-operation with the Directorate of Selection of Personnel, War Office, owned by Central Office of Information, 16 mm. sound, 2185 ft. [660 m.], 35 mm. sound, 5446 ft. [1630 m.], black and white, 56 minutes

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Personnel Selection in the British Army in 1944: Officers

made by Shell Film Unit, 1946, in co-operation with the Directorate of Selection of Personnel, War Office, owned by Central Office of Information, 16 mm. sound, 3591 ft. [1080 m.], 35 mm. sound, 8898 ft. [2670 m.], black and white, 90 minutes.

These two important films are the second and third of the "Report from Britain" series—the first was *Neuropsychiatry*¹. They are made for audiences with psychological training but though their appeal is greatest for psychiatrists they would be understood and enjoyed by anyone interested in the problems of selecting candidates for jobs, or in vocational guidance.

Personnel Selection *Recruits* shows how recruits are assessed during their first two weeks in the British Army so that they may be posted to the type of job for which they are best fitted and in which they will be most useful and happy. The scheme is explained to the recruits by a PSO (personnel selection officer). Then in classes, supervised and guided by sergeant instructors, they do a series of six tests. For one of these, the progressive matrices test, the amount of earlier formal education is unimportant; others, for example an arithmetic test, reflect previous education as well as innate ability and a test of physical agility is included. A test originally designed for clerks only, but found to be more widely revealing and useful, is checking a series of items in two differently arranged lists.

¹ [For review see *BMJ* 77:49—Ed.]

The performances of large numbers of recruits in these tests are referred to and illustrated by a distribution curve. They have been classified into 5 groups, group 1 includes the top 10%, group 2 the next 20%, and so on.

According to the group into which his marks in each of the six tests comes, the recruit completes the battery of tests with six selection group (S G) marks. Each job in the Army has been studied by a "job analysis" to discover the qualities necessary in a man to carry it out. All jobs are grouped into 7 categories, motor-driving, signalling, clerical, general duties, etc., and each of these has minimum SG marks. But these tests do not give enough information for satisfactory posting to the specialized units, and the recruits go on to a further series of tests. In one they have to assemble simple tools such as a bicycle pump, another, which sifts out those suited to be signallers, involves noting similarities in morse sounds.

With their SG marks and special-test results before him, the PSO interviews all the recruits individually, and reviews and corrects the details they have earlier recorded about their education, work records and hobbies. Some recruits are referred to the psychiatrist (two psychiatric interviews are shown in this film). Everyone in the bottom grade of marks sees the psychiatrist, some have given an unfair impression of their qualities, some are mentally quite unsuited for Army life, some will go to make up smart and useful units in the Pioneer Corps, where they are among their peers and not given jobs beyond their powers. The psychiatrist also sees some of the outstandingly good recruits, for the PSO is always on the outlook for men likely to make good officers.

When the recruit has completed his tests and interviews, the PSO considers the results and sums up his qualities and aptitudes and makes first, second and third choice or recommendation of suitable postings for the man. In making these recommendations the PSO is guided by the needs of the Army at the moment, of which he is kept fully informed.

The report sheet on each man with his marks and the PSO's summary and recommendations goes to the War Office and here the data are transferred to a Hollerith punched card. Thousands of these cards are dealt with daily by a sorting machine which at any moment will give the number of men available with various combinations of abilities needed to fill the many units the Army has to keep up to strength.

Personnel Selection Officers shows a group of eight candidates throughout their three-day stay at a WOSB (War Office Selection Board Unit). They have the scheme explained to them and make written answers to question papers ranging over many topics. From these answers a provisional estimate can be made of their capabilities. During the daytime they undergo field tests under military testing officers. Judgment as well as agility is needed for these, some of which are tackled in pairs and some in groups. Sometimes a group is left without a leader to see who provides the initiative, sometimes one of the group is put in charge to see how he can bring out the best of his team. In the evening, discussion-groups are unobtrusively watched by members of the selection Board. Three of the eight candidates are followed more closely and we understand why the preliminary meeting of the board asks that they should see the psychiatrist. Two unrehearsed psychiatric interviews are shown. These sequences are of great interest and they reflect great credit on the director and psychiatrist, for they convey the easy and unhurried way the psychiatrist feels his way from the candidate's remarks to further questions. The relation of the contributions of military testing officers, psychologist and psychiatrist to the work of assessment is conveyed by recurrent animated diagrams throughout the film. The president of the selection board interviews all the candidates himself and when all the interviews and tests are completed the board meets. The shots of this meeting show that while, as in older methods of selection, it is still the president of the board who makes the decision of accepting or rejecting a candidate, he now has not only the opinions of the military testing officers and the impressions gained at his own interviews with the candidates, but also the reports of psychologist and psychiatrist on the intellectual capacity and personality of each candidate. At the end of the course the group are asked for suggestions for improving the methods, and the unsuccessful candidates are told that they may try again at a later date.

These films show a social use of applied psychology which

has obvious large implications in civilian fields, and though they deal with a complex subject, by first-class direction and the wise use of diagrams, they remain (especially the officer film) personal and vivid.

R MacKeith

911

Education of the Deaf

made by Data Film Unit, 1946, owned by British Council, 16 mm sound, 1520 ft [460 m]; 35 mm sound, 4680 ft [1400 m], black and white, 52 minutes

The film starts with a demonstration of the tragedy of the young otosclerotic shut off from her family, and then shows the greater tragedy of the child deaf at birth or rendered deaf in infancy. Without special care, the child would be doomed to be dumb and, therefore, virtually an idiot also. The adult can be helped by suitable deaf-aids selected for her by careful audiometer- and speech-tests, but the child is a more difficult problem. She is sent to a special school when 3 years old, here she learns first of all to copy her teacher's lip-movements, and then to make noises. As time goes on she learns to make speech-like noises, and by the time she is six can speak recognizably a large vocabulary, and understand much simple conversation by lip reading. At seven years of age the class is divided into two halves, those with residual hearing who can appreciate the noise from amplifying earphones, and the totally deaf. Amplifier classes are shown, and then the advanced lip-reading classes, but even here lessons are taken entirely by speech. By 16 years the children have practically the attainments of their normal colleagues. They are taught trades (the school is partially self-supporting from the activities of its trade trainees) and a job is found for them. Many, in spite of complete deafness, have fine singing voices, and dance with a keen sense of rhythm to music they cannot hear. The film ends with a conversation between the mother of the deaf child and a young woman deaf from birth who has trained at this school.

It is an absorbing film, masterfully made with a reserved, unobtrusive technique, in which the sequences are left long enough on the screen for their natural dramatic content to be appreciated. No mention is made of the obviously high incidence of eye-defects among the young children, but clearly these cannot be treated until they have learnt to comprehend and communicate with their doctors. An admirable film, well suited for showing to a wide audience-range the advanced work carried out at the Christie Institute for the Deaf.

Brian Stanford

912

The Development of the Rabbit

made by Gaumont British Instructional, 1943, owned by British Council, 16 mm sound, 1280 ft [380 m], 35 mm sound, 3200 ft [960 m], black and white, 40 minutes

This film is an important contribution to the teaching of embryology, a branch of biology in which films are essential. It gives a clear and interesting account of the development of the rabbit, with references to sea-urchin, trout, frog and chick, indicating the evolutionary background of mammalian embryology.

The reproductive organs of the female rabbit are shown by dissections and supplemented with good diagrams cleverly employed. Diagrams are used to illustrate the liberation of eggs, the passage of sperm along the oviduct, and implantation of the fertilized egg in the uterus. An excerpt from the very remarkable and beautiful Cant film shows cleavage of the living mammalian egg. Early development of the egg and formation of embryonic membranes are described diagrammatically, and of the progressive stages of pregnancy are shown by a series of dissections. The doe is seen eating the placentas of the newly-born young.

The "Development of the rabbit" attains a very high level as an instructional film. Photography is excellent and the judicious use of good diagrams is notable. Two improvements might be made in exposition—several unnecessary technical terms might be omitted, and the essential but unfamiliar vocabulary used in the commentary might with advantage be thrown on the screen.

The film is suitable for elementary biology students. Since it may be used for sex instruction to lay audiences, it must be

pointed out that it has limitations in this respect, its outstanding defect being the omission of discussion of the male reproductive organs. Incidentally it should be made clear that not all animals eat the placenta, lest it may be thought that humans share this habit with rabbits.

Mary Johnson

913

The Life Cycle of Pin Mould

made by Gaumont British Instructional, 1943, owned by British Council, 16 mm sound, 370 ft [110 m.], 35 mm sound, 930 ft [280 m.], black and white, 10 minutes

[Overseas medical teachers and medical societies who wish to borrow or purchase prints of the films indexed or reviewed here should apply to the nearest British Council representative (see page four of cover) or direct to the Editor, quoting the numbers used, e.g. Film 909. Inclusion of a film in this section does not imply that a print will be available for loan or purchase. In some cases it will be, and in others it will not.]

Mary Johnson

Book Reviews

AVIATION MEDICINE

914

Aviation Neuro-Psychiatry

616 8

R N Ironside & I R C Batchelor EDINBURGH E. & S. LIVINGSTONE LTD 1945 viii + 167 PAGES 22 x 14 cm. 8s. 6d. [£0 42s]

(i) The aviator and his environment (ii) selection for flying (iii) flying confidence (iv) the neuro-psychiatric examination (v) the etiology of neurotic reactions to flying (vi) the psychological reaction types (vii) the psychological reaction types—their characters (viii) the psychological reaction types—their prognosis (ix) sickness in the air (x) disturbances of consciousness in the air (xi) neurotic visual disorders (xii) migraine syndrome and other types of headache (xiii) unclassified nervous disorders (xiv) head injuries—their complications and prognosis for flying (xv) prognosis for flying after injuries and diseases of the nervous system Index

The advantages of a systematic psychiatric classification based on causes are so patent and alluring that it is no wonder that unsystematic attempts at creating new causal categories are often made in psychiatry, especially when the cause in question is a prominent and widely operating one. Compensation neurosis has been an instance of this in civilian life, and 'shell-shock' in the 1914-18 war. Aviation, especially in wartime, affords striking evidence of the same tendency. 'flying stress' and 'aeroneurosis' are diagnoses that imply a direct connection between the stresses of flying and the illness to which they may give rise. Such implications have proved unacceptable on clinical grounds, moreover, they have psychological and social consequences which may be detrimental in the same way as 'shell-shock' was. But this does not mean that an all round knowledge of clinical psychiatry gained in ordinary civilian practice will, though indispensable, in itself be sufficient to equip a doctor to deal with the special questions of aetiology, prognosis and treatment that arise in aircrew. As always with psychiatric problems, it is necessary to know the circumstances in which the patient, or the potential patient lives and works and the more intimate the knowledge the better. The application of this to aviation is very plain. Dr Ironside and Dr Batchelor, from first-hand experience in the field, give a straightforward account of the relationship between health and hazards in aircrew. They mention in their preface that the book has wholly been written on service overseas far from libraries the gain in directness, both of style and experience much outweighs any disadvantage arising from this. The first part of this manual deals with flying and the normal individual. A preliminary chapter on physiological difficulties inherent in flying covers chapter on acceleration (especially upon vision and anoxia, the effects of acceleration (especially upon vision and consciousness), cold and fatigue. In the following chapters,

By the use of speeded-up photography, good diagrams and a commentary remarkable for its clarity and absence of technical terms, the observer can get from this film a clear and accurate picture of the life history of a common mould within a few stimulating minutes. The growth of hyphae from spores, and their ramification through the medium, the development of Sporangia and the liberation of spores are beautifully shown. Protoplasmic movements in hyphae and spores can be seen. Diagrams are used to illustrate the fusion of (+) and (-) hyphae and the formation of a resting spore. This is a most successful example of the exploitation of films for teaching biology.

on selection for flying, and on flying confidence, there is little detailed technical information, but much sense. A practical chapter on history taking and methods of examination lead to the body of the book which deals with neuropsychiatric disorders in aviators. By means of concise case records, the variety of clinical pictures is illustrated, and point is given to the discussion of their causation and outcome. The authors make no claim that any of the varied forms of neurotic illness they describe are peculiar to flying, minor effects due to the special circumstances of flying duties occur, but the writers do not admit such a term as aeroneuroses. Chapters on aetiology, symptoms, prognosis, prevention, treatment and disposal are followed by more detailed consideration of sickness in the air disturbances of consciousness, visual disorders, headache, stuttering, somnambulism, and head injury. There is a valuable final chapter on the prognosis for flying after injuries and diseases of the nervous system.

Here and there the book reveals some of the over simplification that is almost inescapable under wartime conditions, for example, the reader might infer from some passages that a neurotic disorder cannot be the direct outcome of a constitutional disability. But the book is intended to be a practical clinical guide, not an exhaustive textbook and it admirably fulfills its purpose.

CHEMOTHERAPY

915

615 778 2s

The Sulphonamides In Theory And Practice

J Stewart Lawrence LONDON H.K. LEWIS & CO LTD 1946 12s. PAGES 21 x 14 cm. 9s. [£0 4s]

(i) Introduction (ii) mode of action and relative potency of the sulphonamides (iii) pharmacology of the sulphonamides (iv) general considerations (v) organisms susceptible to the sulphonamides (vi) regional affections (vii) the sulphonamides in traumatic surgery (viii) toxic effects of the sulphonamides (ix) common abuses of the sulphonamides (x) sulphonamides or penicillin (xi) laboratory tests References Index

Since the introduction of sulphonamides to clinical practice in 1935 there has been such a vast number of papers published about them that the general practitioner (together with most other people who have had reason to handle them) has been in great need of some simple guide to enable him to see the wood among all this multitude of trees. The need was met in part by the memorandum of the Medical Research Council on the Medical Uses of Sulphonamides which embodied the views of most of the British experts on this subject. But this memorandum was (intentionally) dogmatic in form and it did not give systematic references to the literature or indications of the actual results which had been reported after sulphonamide treatment of the different infections. Accordingly there was still a demand for a concise book on the sulphonamides, giving more of the background than the Medical Research Council publication did and such a book has now been produced by Dr Lawrence.

After a brief historical introduction, the mode of action and the relative potency of the different sulphonamides are discussed. The next chapter describes the chemical formulae and characteristics of the sulphonamides now in clinical use, together with their absorption, distribution, excretion and other pharmacological properties. Then the main principles which should be observed in the administration of sulphonamides are considered and a useful table is given, showing the dosage recommended for the different compounds in different circumstances. The following chapter describes the use of sulphonamides against infections by haemolytic streptococci, pneumococci and other organisms sensitive to these compounds. Subsequent sections deal with regional infections, e.g. those of the urogenital tract, with dermatological conditions and with the local application of sulphonamides to wounds and burns. The possible toxic effects of these compounds are described and some abuses in their employment are noted. Finally methods are described for estimation of the concentration of these drugs in body fluids and for testing the sensitivity to them of organisms which have been isolated.

The book is well written and the author has shown skilful judgment in making his account long enough to include a summary of the main reports of each aspect of the sulphonamides but short enough to be readable and easy to consult. He recommends sulphamezathine as the most suitable sulphonamide for routine use, because of its high potency and low toxicity. But sulphadiazine is recommended for all moderate or mild infections and sulphathiazole for severe ones. Sulphapyridine has only a limited sphere of usefulness owing to its toxic effects.

The writer of any book exposes a large area to criticism, and although Dr Lawrence has been very careful there are some points to which objection may be made. Thus, many people may think that he is unduly gloomy in believing that sulphonamides are more dangerous than a general anaesthetic and that some degree of visceral damage is nearly always produced. In the chapter on laboratory tests only a method of estimation by means of *p*-dimethyl amino benzaldehyde is described, it would have been well if the more widely used technique of Bratton and Marshall had also been given. Sulphamezathine was surely first introduced for clinical use by workers at Manchester, even though Roblin may have recorded its examination in the laboratory at an earlier date. There are several other minor misstatements. A more important defect is due to the difficulty of preventing books of this type from becoming somewhat out of date during the interval between composition and publication. In the present instance, few important developments have occurred in sulphonamides during the past two years, but in several fields they have been replaced by penicillin to a greater extent than this book recognizes, e.g. in the treatment of staphylococcal infections, less extensive encroachments on the field for sulphonamides will presumably be made by streptomycin. This defect is only partly remedied by the two pages discussing when to use sulphonamides and when to use penicillin which appear like a patch applied after the main part of the book had been written.

However, these are minor criticisms. The book can be strongly recommended as an account of the clinical uses of sulphonamides which is concise enough to be readable and yet gives a good account of the more important articles on each aspect of the subject. The practitioner will find it easy to consult and clear in its advice as to the action which should be taken in the different circumstances which may confront him.

F Hawking

EMBRYOLOGY

916

611-013

A Class Book Of Practical Embryology

P N B Odgers LONDON OXFORD UNIVERSITY PRESS, 1945
63 PAGES, 30 ILLUSTRATIONS 23 x 17 cm 7s 6d [£0.375]

This laboratory atlas contains a series of 27 line drawings of sections of pig-embryos (6 to 10 mm). Each illustration is faced by a page of descriptive text. The line drawings are on a large scale and are clearly produced in black and white. The book is an admirable supplement to the student's textbook of embryology.

ORTHOPAEDICS

917

Injuries Of The Knee Joint

616.728.3

I S. Smillie, EDINBURGH, E & S LIVINGSTONE LTD, 1944
xi + 320 PAGES, 350 ILLUSTRATIONS 25 x 17 cm. £1 1s. [£1.75]

(i) The importance of the quadriceps, (ii) traumatic synovitis and haemarthrosis, (iii) the surgical anatomy and physiology of the menisci and mechanism of their injuries, (iv) surgical pathology of the menisci, (v) clinical features of internal derangements of the knee joint relative to the menisci, (vi) treatment, after treatment, and complications of injuries of menisci, (vii) injuries of ligaments, (viii) injuries of extensor apparatus, (ix) fractures of tibia and femur involving the knee joint, (x) loose bodies of traumatic origin, foreign bodies, (xi) wounds of knee joint and surrounding tissues, (xii) certain other injuries, (xiii) the stiff knee Index

Mr Smillie's book is a very complete and detailed account of every aspect of trauma of the knee joint. Most of the material is derived from nearly 5,000 cases of knee injury drawn from Service personnel, miners and industrial workers during the years from 1940 to 1945. The book contains much original work by the author and some new ideas which will be of interest, specially to orthopaedic surgeons even if, as the author suggests in his preface, they do not always agree with him.

The author makes a valuable contribution in the emphasis laid throughout the book on the functional result and the importance of bearing this in mind from the beginning of treatment. The importance of early and accurate diagnosis is also repeatedly stressed. It is pointed out that by these means many unsatisfactory end results can be avoided, in particular with regard to injuries of the menisci which have been the cause of a considerable loss of manpower as the result of joints being unable to stand the severe stress of modern battle-training.

The very full chapters on meniscal injuries are excellently illustrated with photographs of every type of lesion, and the extent of the author's material is illustrated by the fact that he can quote 11 cases of complete regeneration of the meniscus and 19 cases of partial regeneration. The author's own operation for repair of the anterior cruciate ligament is described. In it the medial meniscus is detached posteriorly, pared down and threaded through a hole bored in the lateral femoral condyle. For ruptured posterior cruciate ligament a similar operation is described using the lateral meniscus detached anteriorly and passed through the medial femoral condyle. Too few cases have as yet been performed for any definite opinion to be formed, but results appear to be encouraging.

It has been stated that the patella has no important function, but Mr Smillie points out that it serves to carry the extensor tendon away from the centre of rotation of the knee and so increases the mechanical efficiency of the quadriceps. For this reason a more conservative attitude to patella fractures is advocated, and he advises retention of the major fragment in cases where the injury is of moderate degree.

The book is well produced and excellently illustrated. The author is to be congratulated on the line drawings which give the impression of movement with a commendable simplicity of line. The book can be recommended as a complete and stimulating treatise on a very important subject which should be of interest and value to all surgeons.

J W S L

918

617.3(084)

Anatomical Atlas Of Orthopaedic Operations

L S Michaels LONDON, WILLIAM HEINEMANN (MEDICAL BOOKS) LTD 1946 67 PAGES, 73 ILLUSTRATIONS 25 x 17 cm. £1 5s. [£1.25]

This book is intended for quick reference and practical help to the surgeon, in particular one who does not frequently have occasion to perform orthopaedic operations. As such its place may be said to be in the surgeon's room of the operating theatre and, on occasion, in the operating theatre itself.

While not attempting to describe every operation in orthopaedic surgery, it covers a wide field of the standard approaches and procedures. Those which should be of most help to the general surgeon are the approaches to bones, joints and certain muscles.

922

61(092)

while, in addition, the book includes an outline of the more generally practised procedures, such as amputations and incisions of the hand and foot

The description of each operation is short but clearly and concisely set out under the subheadings of position, incision, progress and notes on any particular difficulties that may be encountered. The illustrations are excellent, in particular the coloured anatomical drawings, and the book is well produced and of a practical size and shape. It should be of great value to the practising surgeon and also a very useful reference to the student for the higher surgical degrees

J W S L

TUBERCULOSIS

919

616 24-002 5

Pulmonary Tuberculosis. A Handbook For Students And Practitioners

R Y Keers & B G Rigden EDINBURGH, L. & S LIVINGSTONE LTD., 1945. xii + 273 PAGES 124 PLATES 19 x 12 cm. 17s. 6d. [£0 675]

(i) Historical survey (ii) bacteriology (iii) pathology (iv) epidemiology and resistance (v) symptomatology (vi) examination of the patient (vii) radiology (viii) differential diagnosis (ix) prognosis (x) treatment general principles (xi) treatment collapse therapy (xii) treatment symptomatic (xiii) complications (xiv) after-care (xv) tuberculosis as a national problem Index.

This is a new handbook addressed particularly to students and practitioners of pulmonary tuberculosis at the present time. It includes a full description of the advances in diagnosis and treatment which have been made during the last 20 years. Sufficient information is given to give the student reader a good introduction to the subject while the general practitioner will be enabled to obtain from it an outline of present-day therapeutic measures.

The chapters devoted to the clinical aspect of tuberculosis are the fruits of the authors' considerable experience in sanatoria. The illustrations include a number of excellent skiagrams. Some expansion of the index is called for in a book of this type.

A NEW DICTIONARY

920

61(038)=918 5

Krótki Słownik Lekarski Angielsko-Polski Short Anglo Polish Medical Dictionary

Opracował W Tomaszewski EDINBURGH, L. & S LIVINGSTONE LTD 1945 168 PAGES 14 x 11 cm. 8s. 6d. [£0 425]

This Anglo-Polish medical dictionary, the first of its kind, should be a useful addition to medical literature. During the war the Polish School of Medicine was established at the University of Edinburgh and the need for such a book became apparent. Many who attended that school acquired with their medical knowledge an acquaintance of British medical literature and a better understanding of the English language. For some time Poland will have to look abroad for much of its medical literature and in this connection this little dictionary should prove of value. There are useful supplements dealing with weights and measures symbols signs and abbreviations surgical instruments medical schools and licensing bodies in Britain, prescribing etc.

MEDICAL HISTORY

921

616 89(09)

The Treatment Of Mental Disorders (Ancient And Modern)

Richard Eager LONDON, H. K. LEWIS & CO LTD 1945. 100 PAGES 7 ILLUSTRATIONS. 19 x 12 cm. 7s. 6d. [£0 375]

(i) Historic (ii) the first mental hospital (iii) the King is afflicted (iv) reforms begin (v) the building of the Devon Mental Hospital (vi) early additions (vii) still further extensions necessary in spite of cost (viii) provision for the staff and further minor improvements (ix) the medical staff (x) the nursing staff (xi) the chaplain (xii) artisan staff (xiii) general conditions of patients (xiv) improved treatment (xv) more modern advances (xvi) increasing public interest.

[For review see B.M. 784]

Battling Surgeon

Charles Brook GLASGOW THE STRICKLAND PRESS 1945 176 PAGES PORTRAIT 22 x 14 cm. 2s. 6d. [£0 125]

[For review see B.M.B. 882]

NEW EDITIONS

923

616 71-001 5

A Complete Outline Of Fractures including Fractures of the Skull. For students and practitioners

J Grant Bonnin SECOND EDITION LONDON WILLIAM HEINEMANN (MEDICAL BOOKS) LTD 1946 xiv + 658 PAGES 693 ILLUSTRATIONS 22 x 14 cm. £1 10s. [£1 5]

(i) General (ii) repair of fractures (iii) signs and symptoms of fractures (iv) principles of treatment (v) immediate complications of fractures (vi) late complications of fractures (vii) treatment of wounds (viii) treatment of compound fractures (ix) treatment of non union, delayed union and mal union (x) immediate operative treatment of fractures (xi) war surgery of fractures (xii) apparatus (xiii) plaster of paris technique (xiv) anaesthesia (xv) fractures of the skull vault and base (xvi) fractures of the face and jaw (xvii) fractures and fracture dislocations of the spine (xviii) fractures of the ribs and sternum (xix) fractures of the clavicle (xx) fractures of the scapula (xxi) fractures of the humerus (xxii) fractures of the radius (xxiii) fractures of the ulna and both bones of the forearm (xxiv) fractures and dislocations of the carpus (xxv) fractures of the metacarpals and phalanges (xxvi) fractures of the pelvis sacrum and coccyx (xxvii) fractures of the femur (xxviii) fractures of the tibia and fibula individually (xxix) fractures of both bones of the leg (xxx) fractures of the lower end of the tibia and fibula (ankle) (xxxi) fractures of the tarsus metatarsus and phalanges (xxxii) dislocations of the jaw and upper extremity (xxxiii) dislocations of the lower extremity Appendices Index.

In the five years since this book was first published much experience has been gained in the treatment of fractures, especially the compound variety, and this is embodied in the second edition which has been revised and considerably enlarged by the author, who has himself made his contribution to these advances while serving as orthopaedic specialist with the Army.

Among the additions is a chapter on the operative fixation of fractures, which covers all current methods and contains illustrations of apparatus. The inclusion here of a diagram of Parham's bands might be helpful to the modern student. A useful appendix on operative approaches to bones and joints has also been added. Another new chapter is that on the war surgery of fractures. The author lays down clearly the principle of expert treatment of the fracture as early as possible and, in the meanwhile, treatment of the wound prevention of infection and safe and comfortable evacuation, with a wise warning against primary suture, at any rate by the inexperienced. The Tobruk plaster and thoracobrachial box illustrate this principle and amply justify the space given them though they are unlikely to have any prominent place in peace-time surgery and so should be mainly of historical interest to the coming generations of students.

An adequate account of the use of the sulphonamides, penicillin and proflavine has been added to the chapter on the treatment of wounds. A small omission here is that no mention is made of any adverse effect on the efficiency of penicillin in the presence of other drugs such as oxidizing agents.

The chapter on injuries of the ankle is in itself a monograph on the subject and one feels that the author justifies the inclusion of external rotation as an additional traumatic mechanism. There is no doubt however that it does make the chapter complicated and perhaps difficult for the student.

As with the first edition the book is well written and well produced with excellent illustrations. It can be confidently recommended to all students including candidates for higher surgical examinations and should also be a valuable reference for the practising surgeon.

J W S L

Aleck W Bourns & Leslie H Williams, SIXTH EDITION
LONDON, J & A CHURCHILL, 1945 358 PAGES, 77 ILLUSTRATIONS
20 5 x 13 cm 18s. [1949]

(i) Nutrition in pregnancy and foetal development, (ii) vitamin K and haemorrhagic disease of the new-born, (iii) anaesthesia and analgesia in obstetrics, (iv) breech deliveries, (v) erythroblastosis, (vi) post-natal care, (vii) still birth and neo-natal death, (viii) radiology in obstetrics, by E R. Williams, (ix) cancer of the uterus, (x) sterility, (xi) leucorrhoea, (xii) sympathectomy, (xiii) the sex hormones, (xiv) ovarian tumours, by W Shaw, (xv) radiological investigation and diagnosis in gynaecology, by E R Williams, (xvi) x ray therapy in gynaecology, by W M Levitt Index

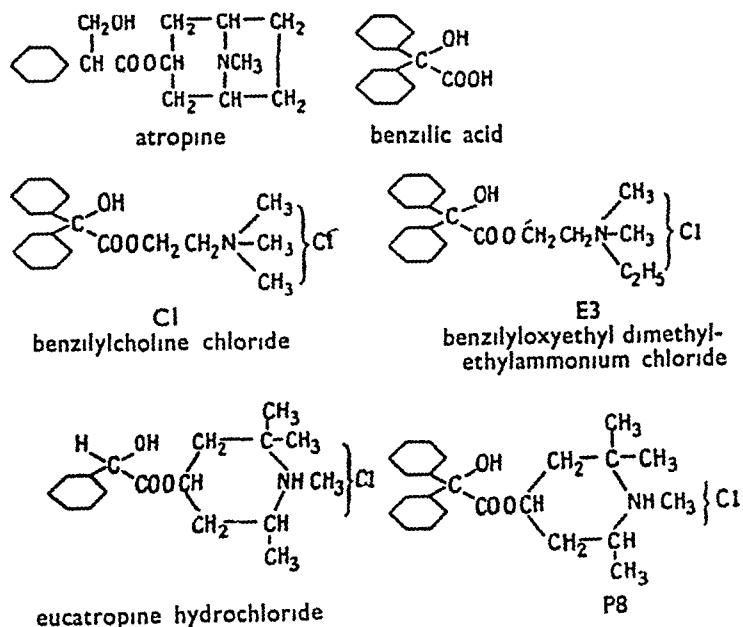
Among the new additions in this latest edition of an old favourite are chapters on nutrition in pregnancy, vitamin K, stillbirth and neonatal death, and erythroblastosis. To make room for them several chapters which have appeared in two or

three previous editions and in which no recent advances of importance have been made, are discarded. The remaining chapters have undergone revision. As the authors point out in their preface, isolated new facts are better in certain annual publications rather than in a book of this kind, it is only when a body of new facts is capable of organic synthesis into a new development or of modifying an accepted line of thought on any subject, that it can claim inclusion in a book of the "recent advances" type. This sentiment is reflected in the present work, which presents an excellent digest of all the significant work which has been recorded in obstetrics and gynaecology during the past few years. Developments in some subjects are so rapid that writers of books of this type cannot hope to be completely up to date in all topics, on account of the interval between preparation and publication, this is noticeable in a few instances in this work. Nevertheless, this book, like most others in the "Recent Advances" series, is to be welcomed.

[The prices quoted are those which obtain within the United Kingdom. Editors of overseas medical journals who wish to review publications of which notices appear are invited to apply to the Editor for review copies, of which a few are sometimes available. Orders for any of the publications mentioned may be sent to the Editor if there are difficulties in obtaining them locally. Publications may be referred to by the numbers given at the left of each item, e.g. Book 914. It should be noted that supplies of all publications are limited and there can be no certainty that publications ordered or requested for review will be available. Publications are classified according to the Universal Decimal Classification and the classification number of each publication is given at the right.]

Corrigendum

FIG 1. FORMULAE OF ATROPINE AND SYNTHETIC SUBSTITUTES INVESTIGATED



Vol 4, No 2

BMB 819, Synthetic substitutes for atropine, H R Ing P 91, col 2, Fig 1 We regret that the names of the compounds of which the formulae were given in this figure were accidentally omitted The figure, including these names, should have appeared as here shown

Addendum

Vol 4,N o 2

BMB 823, p 109, col 2, line 33 After Carden, 1944 insert Humphrey & McClelland, 1944
p 110, col 2 of References, insert Humphrey, J H & McClelland, M (1944)
Brit med J 1, 315

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Background to Chemotherapy

CHEMOTHERAPY has reached a stage at which there is a tendency for general principles to be obscured by a multiplicity of details. This number of the Bulletin is entitled "Background to Chemotherapy" because it is concerned not with the practical applications of chemotherapy, but with some aspects of its historical development and theory. With such an approach to the subject, one of the first questions must be: what is chemotherapy? To this question it is possible to find almost as many answers as there are authorities. Some would exclude, while others include, from the definition the local application of drugs otherwise described as chemotherapeutic. Some would limit the term to the treatment of infections, while others would include the experimental treatment of cancer by chemical compounds. Some would agree with a contributor to this number of the Bulletin, who says that "the use of antitoxins constitutes an important part of chemotherapy", while others would dissent vehemently from this view. Only one conclusion is possible from these conflicting definitions: that the word chemotherapy, as it is currently used, has no precise meaning.

Whatever chemotherapy may be, Ehrlich is by common consent its father, and it is perhaps of interest to consider the sense in which he used the term. In a lecture to the Berliner Medizinische Gesellschaft on 13 February 1907, he said: "What we want is a *Chemotherapia specifica*, that is, we are looking for chemical agents which, on the one hand, are taken up by certain parasites and are able to kill them and, on the other hand, in the quantities necessary for this lethal action, are tolerated by the organism without too great damage." In the same lecture, Ehrlich expanded this notion by referring to the properties of drugs as bacteriotropic—or, more generally, aetiotropic—and organotropic. Drugs were properly described as specific only if their aetiotropy was stronger than their organotropy.

The essence of Ehrlich's conception of chemotherapy was specificity. The conception originally owed nothing to the treatment of infections, but arose from attempts to exploit the affinity of methylene blue for nervous tissue in the treatment of neuralgia. In a paper on "the analgesic action of methylene blue", Ehrlich wrote in 1890 of "cellular therapy" as a consequence of specific cell-nutrition, and added that "only those substances can really influence the cell that are, if the expression may be permitted, eaten by it".

In another paper of 1907 on "Biological therapy", Ehrlich speaks of a *Therapia distributiva*, and in 1913, in his "General address of chemotherapy" at the XVIIth International Congress of Medicine, he lays down as the principle of chemotherapy: *Corpora non agunt nisi fixata*.

Although he had earlier used the term *specific chemotherapy*, Ehrlich came to use the more general *chemotherapy* to express a complex of ideas, which included: first, effective distribution to the seat of action; second, fixation of the drug by the cell or tissue, due to a particular affinity between them; third, and possible only after the fulfilment of the first two conditions, the specific action of some part of the drug on the cell, which was a property distinct from the affinity which resulted in fixation. Because Ehrlich's brilliant conceptions found their most fruitful expression in the treatment of microbial disease, the term *chemotherapy* has come to stand almost exclusively for *specific antimicrobial chemotherapy*, or, more broadly, according to a recent definition (McIlwain, *Biol. Rev.* 1944, 19, 135), for "a subject concerning the properties and the various interactions of drug, parasite, and host".

The simpler idea of chemical sterilization of the infected organism preceded that of specific antimicrobial chemotherapy. Thus, C. Macnamara (*Practitioner*, 1871, 6, 72) only four years after Lister's introduction of surgical antiseptics employed phenol systemically on the ground that it "upon anti-dry-rot principles may protect the body from suppuration". Later, Koch treated animals infected with anthrax by injecting mercuric chloride, but succeeded only in killing the hosts.

From these considerations, we are led to the conclusion that the unqualified term chemotherapy is inadequate. In any branch of science, it is axiomatic that a term should be used by different persons as a symbol for the same thing or idea. Thought and word are inextricably associated, and a looseness or inconsistency of terminology necessarily implies some underlying imprecision of ideas. But whatever may be its most suitable designation, the extent and depth of the subject (or subjects) usually regarded as pertaining to 'chemotherapy' are indicated by the articles which follow.

* * *

BIOGRAPHICAL NOTES

Dr F M LOURIE who contributes an introductory article on the historical development of chemotherapy, is director of the Warrington Yorke Department of Chemotherapy at the Liverpool School of Tropical Medicine. He was formerly associated with Professor S Adler in work on sandflies and leishmaniasis in Palestine, Iraq and Persia, and was then appointed assistant lecturer in protozoology at the Liverpool School of Tropical Medicine. He was a Rockefeller Research Fellow in the University of Chicago from 1931-1933, where he worked on the chemotherapy of malaria in the Department of Professor W H Taliaferro. He later worked again at the Liverpool School of Tropical Medicine, first as a Beit Memorial Research Fellow and then as a member of the scientific staff of the Medical Research Council. During this time he was associated with the late Professor Warrington Yorke in the development of the diamidines as chemotherapeutic agents against protozoal infections [see article by Warrington Yorke on this subject (*BMB* 293)] and for a few years he was seconded to the Colonial Medical Service, in Sierra Leone, West Africa in connexion with a local outbreak of sleeping sickness. On the creation of a department of chemotherapy, as a memorial to Warrington Yorke, at the Liverpool School of Tropical Medicine in 1943, he was appointed its first director.

SIR HOWARD W FLOREY received a knighthood in 1944 and was awarded the Nobel Prize for Medicine, with Dr E Chain and Sir Alexander Fleming, in 1945. A short note on his earlier work appeared in a previous number (vol 2, No 1) of the Bulletin, and his work on antibiotics is too familiar to require mention here. Sir Howard Florey is, at the time of going to press, visiting South America under the auspices of the British Council.

Dr HENRY MCILWAIN is a member of the Scientific Staff of the Medical Research Council, and is at present working in the Council's Unit for Research in Cell Metabolism at Sheffield University. He is also lecturer in biochemistry in the University. His research has been mainly on chemical and biochemical aspects of microbiological problems, commencing in Newcastle and Oxford with the isolation and synthesis of bacterial products. This was followed by investigations of bacterial nutrition, with the Medical Research Council's Department of Bacterial Chemistry (the work of which is described by Sir Paul Fildes, its director, in these columns) at the Middlesex Hospital, London, and by studies of biochemical processes associated with microbial growth, while in Sheffield. Many of the latter investigations have been connected with chemotherapeutic problems and have included studies of the modes of action of several chemotherapeutics. References to these will be found in *Nature*, 1943, 151, 270, 1944, 153, 300, and in *Biological Reviews*, 1944, 19, 135, and subsequent papers in the *Biochemical Journal*. Dr McIlwain is a Fellow of the Chemical Society, and a member of the Biochemical Society and of the Society for General Microbiology.

SIR PAUL FILDES was for many years assistant bacteriologist to the London Hospital under the late Professor William Bulloch. With Bulloch he was the author of the standard work on haemophilia in Karl Pearson's *Treasury of human inheritance* (1911). He was associated with Professor James McIntosh in pioneering the Wassermann reaction and "606" in Britain, and formulated a new outlook on "parasyphilis" with McIntosh and the late Sir Henry Head. On the outbreak of the first World War he and McIntosh turned to anaerobes and produced the McIntosh-Fildes jar. He served in the Navy (Surgeon Lt-Comdr, R N V R) in charge of the Pathological Laboratory at the R N Hospital, Haslar, where he continued to study syphilis, cerebrospinal fever and influenza. In the latter connexion, he designed "Fildes' agar" for the growth of the bacillus, and was one of the first to throw light on the "growth factors" of *B influenzae*. Returning to the London Hospital, he took up the study of tetanus and originated the idea that germination of spores depended upon a suitably low oxidation-reduction potential in the cultures or tissues. This led to the

formation of the Medical Research Council's Unit for Bacterial Chemistry. Fildes was one of the authors of the Medical Research Council's volume, *Diphtheria*, general editor of its *System of bacteriology*, and one of the founders of the *British Journal of Experimental Pathology*, of which he has been editor or director from the beginning. He is a member of the usual pathological societies and a Fellow of the Royal Society.

Dr F R SELDIE was educated at Aberdeen University and after spending a year as House Physician to the late Sir Ashley W Mackintosh, he was awarded the Alexander Anderson Scholarship of Aberdeen University, with which he proceeded to the Pasteur Institute, Paris, to work in the laboratories of Professor C Levaditi from 1929 to 1931. He then became Scientific Assistant to the Director of the Imperial Cancer Research Fund, London, until he was appointed to the staff of the Bland-Sutton Institute of Pathology, Middlesex Hospital, London, in 1936, where he has been assistant pathologist for 7 years. His work with Professor Levaditi was mainly concerned with the pathology and chemotherapy of spirochaetal infections and the properties and pathogenicity of *Spirochaeta moniliformis*. In his later work he has been engaged mainly on chemotherapy, virus studies and cancer research, both independently and in collaboration with Professor James McIntosh who, with Sir Paul Fildes, was the first to introduce salvarsan therapy to Britain. He has recently been working on the development of resistance and other factors which interfere with the action of drugs on bacteria, the treatment of experimental and clinical infections with penicillin, the sulphonamides, the acridines and other drugs, and the phenomena of interference and superinfection in animal virus diseases.

Dr C H ANDREWES is one of the world's principal authorities on virus disease in animals. A note on his work appeared in an earlier number (vol 2, No 12) of the Bulletin.

Dr HAROLD KING is an authority on medicinal substances. He was educated at Bangor University and from 1912 to 1919 worked in the Wellcome Physiological and Chemical Laboratories. From 1919 he has been on the Staff of the Medical Research Council at the National Institute for Medical Research. King has carried out notable work in the field of alkaloids, in particular on hyoscyne and the curare group of alkaloids, in is well known as an investigator on the chemotherapy of trypanosomiasis and of malaria. With Rosenheim he put forward the cyclopentanophenanthrene formula which has revolutionized the chemistry of the sterols, sex-hormones, heart-poisons and related substances.

Dr L P GARROD is bacteriologist to St Bartholomew's Hospital and professor of bacteriology in the University of London. He is particularly well-known for his work on antibacterial drugs, a subject to which he had devoted considerable attention before the introduction of sulphonamides. He has previously been the subject of a note (vol 1, No 3), in this Bulletin to which he has contributed on two previous occasions (*BMB* 48, 197).

Dr J H GADDUM worked under J W Trevan and H H [now Sir Henry] Dale before he became professor of pharmacology in Cairo. He was then appointed to the chair of pharmacology at the Pharmaceutical Society, London, and a few years ago became professor of pharmacology at Edinburgh. He has written papers on the application of mathematical methods in biology and on the use of pharmacological methods for the estimation of substances such as histamine, acetylcholine and adrenaline in the tissues and body-fluids. Most of our present knowledge of the physiological importance of these substances is based on pharmacological assays. The pharmacological department at Edinburgh is now active in this field. Professor Gaddum is the author of a textbook of pharmacology which provides for medical students and others a clear guide to the important principles of the subject. The book was immediately recognized as possessing many advantages and it has in a short time become a standard work.

A SKETCH OF THE HISTORY OF CHEMOTHERAPY

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The word "chemotherapy" means, literally, the use of chemical substances for treating the sick. This would cover a vast field in the practice of medicine, including the use of quite simple compounds such as sodium bicarbonate or aspirin for dyspepsia or headaches, and more complex substances such as vitamins or hormones for deficiency-diseases or endocrine disorders. The term should, however, be restricted in its meaning to the intention of its originator, Paul Ehrlich, that is, to the treatment only of infections (and perhaps cancer) by chemical compounds. As has been well stated by Schulemann (1939), "the investigator in chemotherapy strives after somewhat different aims [from those of the pharmacologist]. He is not concerned with restoring diseased cells to their normal function or with bringing about a reversible alteration of the cell-functions. He aims at reaching the parasite-cells and at throwing their function so irreversibly out of order that the parasite dies but the host remains as unharmed as possible." Chemotherapy is thus at the same time a department of pharmacology and an extension of that subject. It is a part of pharmacology in so far as it is concerned with the action of drugs on the infected subject, and it lies outside a strict conception of pharmacology in so far as it is concerned with the action of drugs on the parasite. In fact, some of the more striking modern advances in chemotherapy derive from studies of drug-action on the parasite, protozoon or bacterium, in the test-tube, isolated from its host, though the ultimate picture can be obtained only by complementary studies both *in vitro* and *in vivo* (McIlwain, 1943a).

Origins of Chemotherapy

Texts on the history of medicine have acclaimed as the Father of Chemotherapy that colourful, robust, hard-drinking, quarrelsome rebel against authority, whose name, in keeping with his flamboyant character, was Aureolus Theophrastus Bombastus von Hohenheim (1493-1541). Generally known as Paracelsus, one account has it that he himself chose this name, with characteristic self-esteem, in order to signalize his parity with Celsus, one of the great physicians of antiquity. The progress of medicine had been delayed for thirteen hundred years by unquestioning servitude to the teachings of Galen, and it was the outstanding service of Paracelsus that he finally broke the bonds of this powerful tradition. He startled and outraged the academic world by inaugurating his appointment as professor of medicine in Basle by publicly burning the works of Galen, and by lecturing in German for all to understand, instead of in Latin for the favoured few. While discarding the doctrine preached by Hippocrates of the four humours—blood, phlegm, black bile and white bile—he reintroduced that great teacher's method of practising as far as possible in the light of experience and exact

observation rather than from the books of traditional authority.

It is perhaps largely because of his vigorous championing of antimony, and other elements, for all manner of ills, and because of his reputed introduction of mercurials for the treatment of syphilis (Garrison, 1929), that claim may be made for Paracelsus as the founder of chemotherapy. However, although he infused some measure of honesty and chemistry, in place of humbug and alchemy, into the practice of medicine, his outlook and methods were inevitably very heavily tainted with the magical and irrational ideas of his age. Indeed, medicine seems, no doubt because of its subjective quality, always to have lagged well behind other sciences in discarding magical precepts. It is significant that the rational approach of Robert Boyle (1627-1691), epitomized in *The sceptical chymist*, earned him recognition as one of the originators of the scientific method, yet, when writing on therapeutics, he could warmly recommend mixtures containing worms, horse dung, human urine, and moss from a dead man's skull (Clark, 1940).

Let us then place Paracelsus as no more than the somewhat cautiously acknowledged grandfather of chemotherapy, whilst having no doubts about referring to Paul Ehrlich (1854-1915) as the father of modern and scientific chemotherapy. With the clear foundations of microbial parasitism introduced by Pasteur (1822-1895), and with his own studies on the chemistry and selective vital staining properties of dyes to build upon, Ehrlich constructed an intricate and ingenious edifice of theory, together with considerable practical achievement. By imagining parasites to be endowed with particular points of attachment, chemo-receptors, with a special affinity for specific drugs, and by embellishing this concept with all manner of improvisations to meet the vagaries of his experimental results, he created a fertile and provocative field for experiment and argument, highly stimulating to subsequent workers in chemotherapy up to the present day. Ehrlich's greatest practical achievement was the introduction of salvarsan (now known as arsphenamine) for syphilis in 1910. This was, however, not the only infection for which a specific remedy was by this time known. Cinchona bark and quinine had already long been recognized as remedies for malaria, and ipecacuanha and emetine had also already been established as specifics for amoebic dysentery. In the field of veterinary medicine, arsenical compounds were already in use for trypanosome infections, and Nuttall & Hadwen (1909) had introduced trypan blue for babesia infections.

The chemotherapy of spirochaetal and protozoal diseases now made great strides, but it was not until the introduction of the sulphonamides by Domagk in 1935 that bacterial infections came well within the range of chemotherapy. This was a turning point in our history, since all previous efforts to devise chemotherapeutic agents against bacterial infections had been so consistently disappointing that the belief was growing that such infections were inherently insusceptible to treatment by chemotherapy. The next and latest high peak of achievement was the discovery of penicillin by Fleming (1929) and of its therapeutic application by Florey (Cham Florey, Gardner, Heatley, Jennings, Orr-Ewing & Sanders 1940). This was the culminating triumph in a long history of the investigation of the by-products of micro-organisms as possible therapeutic agents. Elsewhere in these columns Florey (1946) traces this history as far back as sixty or seventy years ago, when a number of workers, including

Pasteur & Joubert (1877), observing that one micro-organism can elaborate a substance harmful to another of different species, remarked on the potential significance of this for therapeutics. Indeed, there are several contemporary accounts of the successful protection of animals from anthrax bacilli by the inoculation of bacteria antagonistic to these pathogens.

Some Omissions from this Survey

A survey as brief as this must necessarily be highly selective. The first sections below will deal with protozoal and spirochaetal infections, which practically monopolized the field of chemotherapy until the introduction of the sulphonamides, but no account will be given of the chemotherapy of leishmaniasis, in which there have been some spectacular successes, and no further mention will be made of amoebiasis. There will also be no further reference (except in connection with syphilis) to the history of penicillin and other antibiotics, since this is fully covered elsewhere in the present issue of this journal (Florey, 1946). The chemotherapy of helminthic infections, of wounds, and of cancer will also not be mentioned, and, needless to say, in each section below there will inevitably be obvious omissions of much that is important.

The Chemotherapy of Malaria

It seems that we must now abandon the oft-told tale of the introduction of cinchona-bark into Europe by the wife of the Viceroy of Peru, the Countess Anna de Chinchon, after she had been cured of malaria in Lima about three hundred years ago. It now appears that this lady died in Spain before her consort went to South America. The Viceroy's second wife, who was with him in Lima, never suffered from malaria, furthermore, she died on her way home, and therefore cannot be credited with having brought back the bark herself (Haggis, 1941).

Certain it is, however, that Jesuit missionaries and priests played a leading role, from about this period, in the importation of the bark into Europe. In spite of the fact that it was the only true specific known against any disease, its virtues were not universally accepted, and for a very long time there was much bitter opposition to its use. This was probably due partly to the fact that other preparations besides those of cinchona bark were, intentionally or otherwise, frequently confused under the name of Jesuit's bark by the innumerable middlemen engaged in its distribution, and partly to the fact that then, as now, febrile disorders not due to malaria were often wrongly labelled by that name. It was not until the first half of the 19th century that cinchona was fairly generally accepted as a specific for malarial fevers, and quinine and cinchonine, isolated by Pelletier and Caventou in 1820, and the other alkaloids later, were duly recognized as the active agents. About this time nations with Eastern dependencies, in particular the British and the Dutch, became alarmed by the possibility that *Cinchona* species, indigenous only to South America, might eventually become extinct, owing to the extensive felling of forest trees to meet the rapidly expanding demand. There followed, accordingly, a period of intense endeavour by English and Dutch scientists, explorers and adventurers to transfer seeds or plants to India, Java and other countries. These attempts contained all the ingredients of story-book high adventure, including all manner of rivalries, misunderstandings, disguises, frustration, and violence. Details would take far too long to tell, and suffice it to say that success seemed at first to favour the

British, rather than the Dutch. By 1880, the European markets were receiving nearly 20 times more bark from India and Ceylon than from Java (Markham, 1880).

However, the species which grew so well on the Indian plantations, the hardy *Cinchona succirubra*, yields a relatively poor supply of quinine, in relation to total alkaloids, and since the popular demand was specifically for quinine rather than the other alkaloids, these plantations never became an economic success. The eventual ascendancy of the Dutch in this field can be traced to the purchase by their government, for a trifling sum, of a handful of seeds collected in 1865 for an Englishman, Charles Ledger, long resident in Peru. These chanced to be of a type, subsequently named *Cinchona ledgeriana*, which yields an exceptionally high proportion of quinine, but which was very difficult to grow. However, the Dutch succeeded in combining the special virtue of *C. succirubra*, that is its hardiness, with the virtue of *C. ledgeriana*, that is its high quinine-content, by the simple expedient of grafting the one upon the other, the success of the Java cinchona plantations is, in fact, said to be based on the grafting of millions of *C. ledgeriana* scions on understocks of *C. succirubra* (Taylor, 1945). By the outbreak of the first world war the Java plantations were supplying about 95% of the world's quinine.

In time of war the importance of adequate means of treating malaria is paramount. In 1916, for example, General Sarrail had to report, at a critical period, that his army in the Balkans was immobilized in hospital on account of malaria (Sergeant & Sergeant, 1932). This was representative of the situation in many theatres in malarious countries, and it is not too much to say that the supply of quinine was one of the essential features upon which the outcome of the first world war depended. After the war an intensive search for synthetic antimalarials was conducted in Germany. With the aid of a technique devised by Roehl (1926) for testing antimalarial activity in canaries, the first notable success was scored in 1924 by the discovery of plasmochin, now known as pamaquin (Schulemann, Schonhoffer & Wingler, 1932), and this was then followed by the more valuable atabrin, now known as mepacrine (Maus & Mietzsch, 1933).

On the outbreak of the late war, British manufacturers immediately turned their attention to the large-scale production of mepacrine, which, till that time, was a German monopoly. The success of these efforts was one of the deciding factors in winning the war, since the Japanese occupation of Java, with its cinchona plantations, in 1942, immediately threw the armies of the United Nations into jeopardy because of the probability of eventual exhaustion of quinine-supplies, if the war were to last long enough. There followed an anxious period, for whilst it was known that long-continued "suppressive" treatment by quinine is not only safe but would not impair the efficiency of armies in the field, this had not yet been established for mepacrine. Several outbreaks of illness among troops in the field were, in fact, at the time, suspected to be due to the toxic effects of "suppressive" mepacrine treatment, and it became urgently necessary to define exactly the potentialities and dangers of this compound. Its safety and value as a suppressive against all forms of malaria under active service conditions were in due course triumphantly vindicated, and Hamilton Fairley (1945) has described how, among the Australian Forces in New Guinea, for example, its regulated use contributed to a reduction of malaria incidence from 740 per 1 000 per

year in December 1943 to 26 per 1,000 per year in November 1944, with a death rate of less than 1 in 3,000

However, there were weighty reasons for a determined search for alternative antimalarials. It was not safe merely to wait for the value of mepacrine to be proved, and among other disadvantages eventually confirmed was the fact that benign tertian malaria is not cured by mepacrine but merely suppressed, only to recur later. Intensive research was therefore pursued in Britain and America, and the most striking result was that achieved in the discovery of paludrine, as the result of an entirely new approach in the search for antimalarials, by Curd, Davey & Rose (1945). It was not possible to obtain canaries in sufficient numbers for routine tests on all the innumerable compounds synthesized, and a method was devised for using young chicks infected with *Plasmodium gallinaceum*, in the preliminary sorting out of potential antimalarials, with resource to other types of malarial infection in chicks and canaries as required.

The hypothesis of James (1931) was adopted, that the inability to effect causal prophylaxis (or radical cure) in benign tertian malaria in man is due to hitherto undemonstrated exo-erythrocytic stages of the parasite, such as were later demonstrated for *P. gallinaceum* (James & Tate, 1937, Huff & Coulston, 1944). The efforts of Curd, Davey & Rose therefore took the direction urged by James (1937), namely, to find a drug which acts not only against the forms occurring in the erythrocytes—and therefore perhaps as a suppressive, or as an ameliorative agent in man—but which acts also against the exo-erythrocytic stages in the bird-infections, and hence as a possible causal prophylactic or radical curative agent in man.

Most of the very considerable synthetic work of earlier investigators in the search for antimalarials had concentrated on variations of either quinoline (as in quinine and plasmoquin) or acridine (as in mepacrine), considerably less attention having been paid to other heterocyclic ring systems. Curd, Davey & Rose, however, chose at the outset to explore the possibilities of the pyrimidine nucleus, for a number of novel reasons, and their researches soon led them to lay considerable stress on the conclusion that one of the determinants of antimalarial activity is a molecular configuration which allows of certain types of tautomeric change. It followed from this that if, in pyrimidine compounds selected as exhibiting a high degree of antimalarial activity, the pyrimidine ring were broken in such a way as to leave undisturbed the tautomeric possibilities, antimalarial activity might be retained. On this reasoning the pyrimidine nucleus was discarded, and biguanide compounds emerged, one of which is paludrine, first tested in man by Adams, Maegraith, King, Townshend, Davey & Havard (1945) and Maegraith, Adams, King, Townshend, Davey & Havard (1945). It is too early for this substance to have established its final place in the treatment of malaria, but it is notably non-toxic and acts on all three of the main forms of human malaria. Like mepacrine (but probably more readily), it can prevent infection from becoming established and is a radical cure in malignant tertian, but apparently not always in benign tertian, malaria.

The Chemotherapy of Syphilis

Ehrlich's original experiments leading to the discovery of anti-syphilitic remedies depended on tests against infections in mice caused not by spirochaetes but by trypanosomes, and his eventual introduction of arsphenamine in 1910,

followed by neoarsphenamine in 1912, may actually be traced to the demonstration by Wolferstan Thomas in 1905 that an arsenical, atoxyl, is effective against trypanosome infections. It was then shown by Ehrlich & Bertheim (1907) that, contrary to an earlier belief, atoxyl consists of *p*-amino-phenylarsonic acid, and there followed the well-founded theory, based on studies *in vitro* (Ehrlich, 1909a), that the activity of this substance is attributable to its reduction to the corresponding arsenoxide form.

However, Ehrlich did not urge the use of phenylarsenoxide analogues in man, believing them to be too toxic. If atoxyl or similar substituted phenylarsonic acids, be still further reduced, beyond the arsenoxide stage, arsenobenzene derivatives are obtained, and it was among these that arsphenamine and neoarsphenamine were found. Like the arsonic acid prototype, the arsenobenzene form is believed to be relatively inactive, its parasitocidal effect coming into play only on oxidation to the corresponding arsenoxide form (Voegtlin & Smith, 1920).

In recent years (Foerster, McIntosh, Wieder, Foerster & Cooper, 1935) the idea has been revived of employing the active form, i.e. the phenylarsenoxide, in the treatment of syphilis, rather than its inactive precursors, the phenylarsonic acid or arsenobenzene forms, and *m*-amino-*p*-hydroxyphenylarsenoxide (mapharside, neohalarsine) is now very widely used. It is more toxic to the host than the other forms, weight for weight, but this is offset by its exceptional toxicity for the parasite, so that quite small doses, normally well within the range of safety for man, are efficacious. Phenylarsonic acids are not used for early syphilis but one compound of this type, trypanarsamide (see under *Trypanosomiasis*), has found an important place in the treatment of neurosyphilis, because of its powers of penetration into the central nervous system, in which location it presumably exercises its effect upon being reduced to the arsenoxide form (Hawking, Hennelly & Quastel, 1937).

Ehrlich's hope was that with arsphenamine or neoarsphenamine he might achieve his ideal of "therapia sterilisans magna"—that is eradication of infection by means of a single dose. It soon became clear, however, that for the treatment of human syphilis by these and related compounds repeated injections are necessary, preferably together with bismuth, in courses extending over many months. Such courses are, of course, exceedingly irksome, and the effect is that considerable numbers of patients do not complete their treatment. Marshall (1944), for example, states that not even half the patients who begin these long courses of injections persevere long enough to ensure a cure-rate of more than 80%. With the object, therefore, of reducing the duration of treatment to the absolute minimum, i.e. to approach as closely as possible to Ehrlich's "therapia sterilisans magna," short term schemes of intensive therapy by intravenous drip were introduced by Chargin, Leifer & Hyman (1935). Their original technique employed neoarsphenamine during a 5-day period, but this proved to be too toxic, and considerable modifications by innumerable investigators have since been explored, including the use of mapharside instead of neoarsphenamine rapidly-repeated injections of massive doses instead of intravenous drip, and variations in the duration of treatment.

A new era in the treatment of syphilis was inaugurated by the discovery of the activity of penicillin in spirochaetoses. The demonstration of therapeutic action against *Spirochaeta recurrentis* and *Spirillum minus* infections in mice suggested

that the substance might be effective against syphilis (Lourie & Collier, 1943), but the first cases to be actually treated were investigated in the United States (Mahoney, Arnold & Harris, 1943). The great advantages are complete freedom from serious toxic effects, and short duration of treatment such as has been aimed at by the schedules of intensive arsenotherapy, but it is too soon for final judgments to be passed.

The Chemotherapy of Trypanosomiasis

The discovery of atoxyl as a therapeutic agent against trypanosomiasis by Thomas in 1905 did not mark the beginning of arsenical therapy in these infections. Inorganic preparations, such as sodium arsenite, had been used with somewhat indifferent success since long before the recognition of trypanosomes as the cause of nagana in cattle and of sleeping sickness in man (Braid, 1858, Livingstone, 1858). After the demonstration of the activity of atoxyl, a number of Ehrlich's arsenobenzene compounds, which he synthesized as much with a view to sleeping sickness as to syphilis, were given a trial in Africa. Thus, arsphenamine and neo-arsphenamine were considerably used, and one of the most promising of this series was arsenophenyglycine (Ehrlich, 1909b). A special virtue of the latter was that, unlike other arsenicals, it was effective against trypanosomes which had developed drug-resistance as a result of insufficient treatment by atoxyl, arsphenamine, or any of a considerable range of arsenicals. (The recently introduced *p*-arsenophenylbutyric acid compound of Eagle (1945) also exhibits this property, which Ehrlich (1909b) found to be shared by those arsenicals which contain an acetic acid radical.)

However, whilst most of these arsenobenzene derivatives were effective in the early stages of infection, they were eventually judged to be of little or no use once the central nervous system had become invaded. The introduction of tryparsamide by Jacobs & Heidelberger in 1919 was therefore a great step forward, since it provided a drug which is often curative in cases of cerebral involvement, although it has the disadvantage of sometimes giving rise to optic atrophy, especially in the very type of case in which its use is most called for, i.e. where the infection has reached an advanced stage.

Whilst arsenicals are, on the whole, highly efficacious against *T. gambiense*, they are of considerably less value against *T. rhodesiense*, sleeping sickness, and there has therefore always been a need of alternative remedies. One of Ehrlich's earliest triumphs in chemotherapy, directly arising from his studies of the selective affinities of living matter for dyestuffs, was the demonstration of "therapia sterilisans magna" against trypanosome infections in mice by an azo dye derivative of naphthalene and benzidine—trypan red (Ehrlich & Shiga, 1904). This did not prove to be of practical value in man or domestic animals, but it gave a lead to the production and examination of a very long series of related compounds, not all dyes, culminating in 1920 in the announcement of Bayer 205 (now known as suramin, or antrypol), a non-staining complex urea derivative.

The exceptionally high therapeutic index of this compound (Haendel & Joetten, 1920, Mayer & Zeiss, 1920) in infected mice seemed to give promise of outstanding efficacy in man. Its discovery was therefore announced with considerable fanfare, the secret of its composition was jealously guarded, and its potential value to Africa was apparently thought in some German circles to be of such a sensationally high order that Germany's forfeited colonies should be restored (Pope,

1924). With considerable ingenuity, which it was necessary to exercise no less in order to obtain the drug for analysis than in its actual examination, Fournieu, Trefouel & Vallee (1924) elucidated and announced its composition, and this was confirmed some years later by the Germans.¹ It is now known to be of value only in early cases of sleeping sickness of both the *gambiense* and the *rhodesiense* type, and is useless after the central nervous system has become involved.

A new class of trypanocidal compounds was discovered in the aromatic diamidines. The lead to this was given by the finding of von Jancso & von Jancso (1935) and Schern & Artagaveytia-Allende (1936) that synthalin (decamethylene-diguanidine) is effective against trypanosome infections in mice. Synthalin had previously been introduced into medical practice as a means of reducing the blood-sugar in diabetes, and since it was known that trypanosomes consume large amounts of glucose, the von Jancsos and Schern believed that the therapeutic effect of synthalin in trypanosome infections was mainly due to the fact that the parasites were deprived of glucose as a result of hypoglycaemia produced in the host. However, Lourie & Yorke (1937) showed that synthalin exercises an exceedingly powerful direct action on trypanosomes *in vitro*, and, moreover, insulin, which reduces the blood sugar *par excellence*, has no action on trypanosome infections. This led to the examination of a series of other guanidines, and then to related isothioureas, amines, and amidines (King, Lourie & Yorke, 1937), resulting in the eventual selection of certain aromatic diamidines, such as pentamidine, as the most promising (Lourie & Yorke, 1939). Like suramin, these compounds have proved to be highly effective in early, but not in late, *gambiense* and *rhodesiense* sleeping sickness.

The most important trypanosome infection of cattle is that caused by *T. congolense*. This is notoriously refractory to arsenicals and other compounds of proved value in human trypanosomiasis, but there is considerable promise here in the phenanthridinium series, introduced by Browning, Morgan, Robb & Walls (1938).

The Sulphonamides

Dyestuff chemistry played an important part in the inception of sulphonamide-therapy, as it had already done in the development of the chemotherapy of protozoal infections. The sulphonamido group had long been known to increase the fastness of acidic dyes to washing and to light. In 1932, Mietzsch & Klarer introduced this group to the dye chrysoidin, which had already been found by Eisenberg (1913) to exercise some antibacterial activity *in vitro* but not *in vivo*, and the resulting compound, *p*-sulphonamido-chrysoidin, or prontosil, was announced by Domagk (1935) as an effective agent against infections with haemolytic streptococci. It was then shown by Trefouel, Trefouel, Nitti & Bovet (1935) that the part of the prontosil molecule which conferred staining properties was in no way essential to its therapeutic powers, which were equally displayed if the substance were abbreviated to *p*-amino-benzenesulphonamide (commonly known as sulphanilamide).

The numerous sulphonamide drugs which have since been introduced into practice, selected from many hundreds synthesized towards this end, are merely substituents of sulphanilamide. In the earlier compounds, substitution was in the amino group (as in benzyisulphanilamide), these depend for their activity on being hydrolyzed in the body to

¹ [See also B14B 934—ED.]

sulphanilamide. In the later and more effective compounds substitution was in the amide group (as in sulphapyridine, produced by substitution with pyridine), and they exercise their effect direct without being converted *in vivo* to sulphanilamide. Still more recently, compounds have been introduced in which substitution is both in the amino and the amide group. Such are succinylsulphathiazole (sulfasuxidine) and phthalylsulphathiazole (sulfathalidine), which have a special place in the treatment of infections of the intestinal tract, where they are slowly broken down to the effective component, sulphathiazole.

It is not possible in such a short review to mention even the names of all the more important sulphonamides, still less to describe the stages by which they have found their level in therapeutics. The crude generalization must suffice that the action of sulphanilamide and its immediate successors was found to be mainly directed against haemolytic streptococci, *B. coli* (in urinary infections), meningococci and, to a less extent, gonococci. With sulphapyridine (Whitby, 1938), pneumococci also came to be covered, and the action on gonococci was improved, and with sulphathiazole (Herrell & Brown, 1939) and sulphadiazine (Feinstone, Williams, Wolff, Huntington & Crossley, 1940), the range widened still further to include staphylococci, though the latter are not as spectacularly susceptible to any sulphonamide as they are to penicillin.

Modern Theories of Drug Action

The development of sulphonamide-therapy naturally gave a considerable impetus towards the formulating of rational conceptions of the mode of action of chemotherapeutic agents in general, including drugs other than sulphonamides. Ehrlich's theories of drug-action did recognize that the attachment of a chemotherapeutic substance to its appropriate "receptor" on the parasite cell interferes fatally, in an undefined way, with the nutritional state of that cell. Nevertheless, as McIlwain (1943b) has pointed out, these theories were conceived without relationship to contemporary developments in biochemistry. There seems to have been no attempt by Ehrlich to identify his drug-receptors with enzymes or their substrates, although much was already known which might have suggested such an identification.

The newer orientation of ideas was concisely stated by Fildes (1940) along the following lines². Chemotherapeutic agents are considered to act by interfering with a metabolite essential for the parasite's growth, the drug exercises this interference-effect (i) by oxidizing a substance which requires to be reduced, or (ii) by molecular combination, forming

an inactive product, or (iii) by competition for an enzyme associated with utilization of the metabolite by the parasite. For mechanism (iii), the chemotherapeutic compound would characteristically be so similar structurally to the essential metabolite that both would fit the same enzyme. In the field of general biochemistry examples had long been known of such interference with enzyme reactions, by the interposition of compounds structurally akin to the natural substrate or co-enzyme concerned, and the classical instance of this in chemotherapy was provided by Woods in 1940.

It had been known since the work of Colebrook, Buttle & O'Meara (1936) that, contrary to earlier theories, sulphonamides exercise a direct deleterious action on bacteria, without mediation of the host. It was also known, however, that this action could be antagonized by certain bacterial extracts or body-fluids (see especially Stamp, 1939, Green, 1940). Woods' outstanding contribution was to show that this antagonism can be effected specifically by *p*-aminobenzoic acid, structurally very similar to sulphanilamide, and much subsequent work has borne out his interpretation that sulphanilamide acts by blocking the enzymes which subserve to the utilization of *p*-aminobenzoic acid essential to the parasite's nutrition.

The conception has been pursued that the growth of bacteria may be inhibited by substances structurally similar to metabolites essential for the nutrition of those bacteria. For example, analogues of the essential metabolites nicotinic acid and nicotinamide have been found to be inhibitory to bacteria *in vitro* (McIlwain, 1940). The principle has been beautifully applied in the actual discovery of a new chemotherapeutic agent, it was argued *a priori* that pantoyletaurine, structurally similar to the essential metabolite pantothenic acid, should be able to exercise chemotherapeutic properties against infections of haemolytic streptococci in rats, and this was, in fact, found to be the case (McIlwain & Hawking, 1943). The chemotherapeutic effect was not of a very high order, but the value of the work is that it was a radical departure from the time-honoured technique of "hit or miss", in the search for new chemotherapeutic substances. In the past a particular chemical group may have been suspected or shown to exercise some activity against a particular infection, and the common procedure was then to synthesize hundreds—perhaps thousands—of compounds of that group, and to test each in turn, in the hope of striking upon a really useful chemotherapeutic agent. But in McIlwain & Hawking's demonstration of the chemotherapeutic effect of pantoyletaurine, the results were fairly exactly anticipated, by prior biochemical observations on both host and parasite, with the clearly-defined aim of preventing the parasite from utilizing a known metabolite essential for its existence.

² [See also BMB 929—Ed.]

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STEPS LEADING TO THE THERAPEUTIC APPLICATION OF MICROBIAL ANTAGONISMS*

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In many countries there is now proceeding extensive search for new antibiotics, investigation into the nature of their structure and biological properties, and research into the susceptibility of various infections to them. The impetus to the search has become much greater since it was shown at Oxford in 1940 that one of them—penicillin—was not only an antiseptic but a chemotherapeutic agent, that is, a drug which can be administered so as to circulate in the bloodstream in sufficient quantity to cause infecting organisms to die or at least to cease multiplication, while at the same time the body-tissues are not harmed. The work of the last few years, however, is only an expansion of studies in which, since the time of Pasteur, bacteriologists, botanists and other scientific workers have been engaged.

Although the use of the word "antibiotic" to mean the actual chemical substances involved in bacterial antagonism was only recently introduced by Waksman, Horning Welsch & Woodruff (1942), the observation of antagonisms

between bacteria, and even the idea that one bacterium might thus be used to combat another, has frequently occurred. Vuillemin wrote in 1889

"Nul n'a traité de parasite le lion qui fond sur sa proie, ou le serpent qui instille du venin dans la plaie de sa victime avant de la dévorer. Ici, point d'équivoque: un être détruit la vie d'un autre être pour entretenir la sienne. Le premier est complètement actif, le second est complètement passif: celui-ci est sans restriction contraire à la vie de celui-ci. Le cas est si simple qu'on n'a jamais songé à lui donner un nom. Cette condition au lieu de s'offrir isolément à notre examen, peut se présenter comme facteur de phénomènes plus complexes. Pour simplifier le langage, nous l'appellerons alors *antibiose*, l'individu actif sera l'*antibiote*, l'individu passif sera le *support*."

"Antibiosis" finally came to mean the interference with the growth of one micro-organism by another. Thus we arrive at the modern word "antibiotics" as the name for the chemical substances, products of metabolism, which are frequently involved in this antagonism. But long before the adoption of these terms, people of Central Europe, the Ukraine, Central America, and possibly of other countries, deliberately grew moulds, probably of the kinds called *Penicillia*, to be used as applications to wounds. The taking of yeast was advocated in 1852 by an English practitioner Mosse, for the treatment of boils—a treatment which had already been used in the north of France, and is even now still in use, but as the yeasts have never been clearly shown to produce any definite chemical substance combating pathogenic organisms, any beneficial effect from them is possibly caused by their vitamins.

First Scientific Observations

The first demonstration of antibiotic action against a pathogenic organism was made by Pasteur and his colleague Joubert in 1877. They observed that if a culture of anthrax

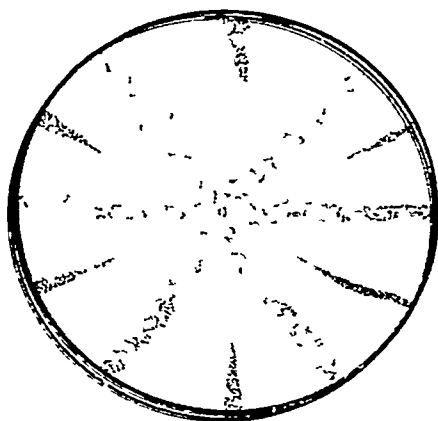
* Based on the Lister Memorial Lecture which was delivered at the Royal College of Surgeons on 11 October 1945 and published in the *British Medical Journal*, 1945, 2, 635-642. The present paper contains additional material from several subsequent lectures.

bacilli in urine was contaminated by organisms from the air the anthrax bacilli were destroyed

"L'urine, ai je dit, neutre ou legerement alcaline, est un excellent terrain de culture pour la bacterie, que l'urine soit pure et la bacterie pure, et dans l'intervalle de quelques heures, celle-ci est tellement multipliee que les longs filaments qui la composent remplissent le liquide d'un feutrage d'aspect cotonneux, mais si, au moment de depoter dans l'urine les bacteries a titre de semence, on sème en outre un organisme aerobie, par exemple une des bacteries communes, la bacterie charbonneuse ne se developpe pas ou tres-peu, et elle perit entierement apres un temps plus ou moins long. Chose bien remarquable, ce meme phenomene se passe dans le corps des animaux qui sont le plus aptes a contracter le charbon et l'on arrive a ce resultat surprenant qu'on peut introduire a profusion dans un animal la bacterie charbonneuse sans que celui-ci contracte le charbon, il suffit qu'au liquide qui tient en suspension la bacterie on ait associe en même temps des bacteries communes. Tous ces faits autorisent peut-être les plus grandes esperances au point de vue therapeutique."

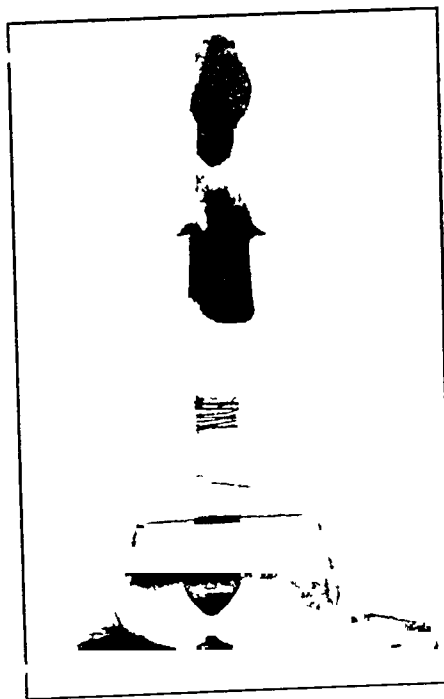
Pasteur and Joubert thus found that by introducing some common bacteria into the animal body at the same time as the anthrax bacillus, the death of the animal from anthrax could sometimes be prevented. As Pasteur was at the time mainly interested in immunity, he did not pursue the matter. In 1885, Babes demonstrated on solid as well as in liquid media that one organism can elaborate a substance which will stop the growth of another, and suggested that "L'etude continuee et generalisee de cette action reciproque des bacteries les unes vis-a-vis des autres, pourra conduire a des donnees therapeutiques." He correctly deduced from his experiments that the inhibitions of bacterial growth he had observed were brought about by a definite chemical substance produced by the antagonistic organism. In the same year Cantani (1885) evolved the idea of replacing a harmful

FIG 1 A METHOD, WHICH IS STILL IN USE, OF DETECTING BACTERIAL ANTAGONISM (Frost, 1904)



Frost writing in 1904 gave this illustration of the method which had first been described by Garre in 1887. *Ps. fluorescens* was planted on the surface of an agar plate in 6 radial streaks and the plate was incubated for 24 hours to give time for metabolites to be produced and to diffuse through the agar. *B. typhosus* was then planted in radial streaks alternating with those already grown. After further incubation it was apparent that *Ps. fluorescens* had produced an inhibitor which had prevented the *B. typhosus* from growing except at the periphery of the plate where the streaks were furthest apart.

FIG 2 A METHOD OF TESTING ANTAGONISM BETWEEN BACTERIA IN FLUID CULTURE MEDIA (Frost, 1904)



The effect of one fluid culture on another was tested by separating the cultures by a substance permeable to metabolites but not to bacteria. Previously this had been done by putting one culture inside and the other outside a Pasteur Chamberland filter. Frost modified the method by enclosing one culture in a collodion sac and suspending the sac in a flask containing the other culture. In the experiment which he illustrated the sac contained *B. typhosus* and the flask the opposing organisms. Certain unidentified soil bacteria killed 98% of the *B. typhosus* in 6 days.

organism (the tubercle bacillus) in the tissues of the lungs with an ill-defined harmless organism (which was probably a mixture of species) called *Bacterium termo*. He treated a tuberculous patient by insufflating large amounts of cultures of this bacillus into the lungs, and claimed good results. This was the first example of the idea of the replacement of one pathogenic organism either by another less pathogenic or, if possible, by an innocuous organism, an idea which frequently recurs in subsequent pathological and clinical literature.

Two years later the Swiss, Garre (1887), introduced a method for examining bacterial antagonism by means of alternating streaks of two species of bacteria grown on a Petri dish containing agar—a method essentially the same as some of those still in use. Garre wrote

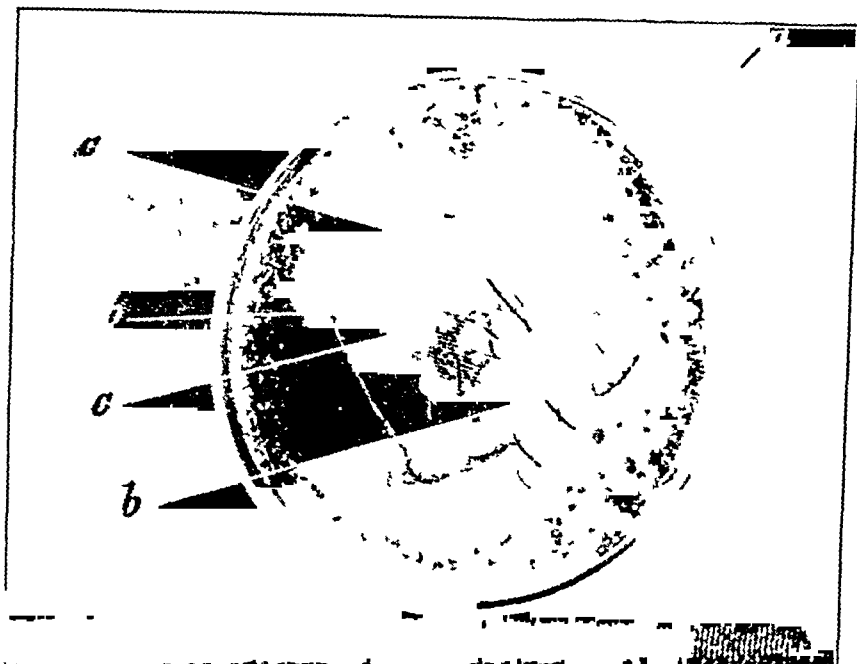
"Auf die brach erkaltete Platte impfe ich gleichzeitig in parallelen Strichen alternierend den *Bac. fluorescens* und den *Staph. pyog*—so zwar, dass zwischen die Distanz der Impfstiche grosser wird, von 3-15 mm. Der *Bac. fluorescens* wächst rascher, seine Ausscheidungsproducte diffundiren in die Umgebung und werden für die näher gelegenen *Staphylococcus*impfungen zum absoluten Entwicklungshinderniss. Es handelt sich also nicht um ein Ueberwuchern und Verdrängen der einen Art durch die andere, rascher sich ausbreitende,—wie etwa in einem Garten üppiges Unkraut zarte Pflänzlinge ersticken kann. Es ist auch kein

Vorwegzählen der disponibeln Nahrung durch rascher keimende Mikroorganismen, sondern es liegt hier ein Antagonismus durch Ausscheidung spezifischer, leicht diffundirender Stoffe vor, die für die einen Arten ein Entwicklungshinderniss bilden, für die andern aber durchaus indifferent sind"¹

Garre's paper was not illustrated, but in 1904 Frost described seven methods for the investigation of the antagonistic properties of bacteria, and among these was Garre's method, of which Frost published an illustration (Fig 1). One of the most interesting methods described by Frost is that in which he grew one bacterium in liquid medium in a flask and another in medium contained in a collodion sac suspended in the flask, an antibiotic produced by the bacterium in one medium could diffuse through the collodion and inhibit the bacterium in the other (Fig 2).

The first photographic record of the phenomenon of antibiosis was published in 1889 at Kiel in a thesis by Doehle (Fig 3). This illustration—the photograph for which was

FIG 3 THE FIRST ILLUSTRATION OF ANTIBIOTIC ACTION (Doehle, 1889)



Doehle poured a plate of gelatin medium containing anthrax bacilli. On the surface he planted, in a square, a coccus to which he gave the name *Micrococcus anthracotoxicus*. After incubation the anthrax bacilli had grown in the peripheral part of the plate (a), but both outside and inside the square formed by the *Micrococcus* (b) the anthrax bacilli had failed to grow (c).

actually taken by Hoppe-Seyler himself—shows the anthrax bacillus, which had been sown in a solid medium, being inhibited in the neighbourhood of a certain micrococcus, which Doehle had isolated and called *Micrococcus anthracotoxicus*, planted in the form of a square.

Thus, by 1889 the phenomenon of microbial antagonism was well known and had been illustrated, and not only

¹ I inoculated on the untouched cooled [gelatin] plate alternate parallel strokes of *B. fluorescens* and *Staph. pyogenes*. This was carried out so that the distance between the inoculated strokes increased from 3 to 15 mm. *B. fluorescens* grew more quickly. Its products of secretion diffused into the surroundings and were completely inhibitory for the near by staphylococcal inoculation. Thus it is not a question of overgrowth or crowding out of one by another quicker growing plants, but of an antagonism caused by the secretion of the available foodstuff by the more luxuriantly growing weeds kill the delicate plants which are inhibitory to the growth of some species but completely ineffective against others.

Pasteur, but nearly all the bacteriologists who worked on it at that time, had in mind its use for therapeutic purposes. Emmerich, for instance, in 1887 had shown that some effect could be obtained in protecting rabbits from experimental anthrax by the simultaneous injection of a streptococcus from a case of erysipelas. Clinicians had long believed that an attack of erysipelas was beneficial in certain chronic infections, and in 1883 Fehleisen had deliberately treated a case of lupus by injecting streptococci from a patient with erysipelas. Emmerich, however, demonstrated that there was no antagonism between the two organisms *in vitro* on the surface of a solid medium, so he ascribed his results to stimulation by the cocci of the body-cells, which were then able to demolish the bacilli.

Pyocyanase and its Clinical Utilization

The most promising attempt at the therapeutic use of a natural antibacterial substance was started by the work of Bouchard in 1889. He observed that the injection of a culture of *Ps. pyocyanea* could confer some degree of protection on rabbits infected at the same time with anthrax. Metabolic products of the bacteria were next used instead of whole cultures, and trials on man of "proteins" from cultures of *Ps. pyocyanea* were made ten years later by Honl & Bukovsky (1899).

Meanwhile, Emmerich and Low were independently working with the same organism, and in 1899 they prepared from old cultures of *Ps. pyocyanea* an extract which they called pyocyanase, capable of lysing suspensions of *B. anthracis* *in vitro*, and also bactericidal to *Bact. typhosum*, *C. diphtheriae*, staphylococcus, and *P. pestis*. At first they attempted systemic administration of pyocyanase in experimental infections in animals, but it proved too toxic and eventually was used only as a local application to infected parts. Its clinical use for many infections by local application was widespread for some time, but by about 1912 or 1913 had practically ceased, apparently because the commercial preparations made at that time were inactive. Although Emmerich and Low seem to have confused the antibiotic effect of the substance with the views on immunity held at that time, the work with pyocyanase was the first serious attempt to use a bacterial product or antibiotic in medicine for curative purposes.

The important idea of differential toxicity, which so largely governs the choice of antiseptics today, must

have been widespread at that time, for Escherich wrote in 1906

"Die Wiederaufnahme dieser Bestrebungen wurde erst möglich, als die Fortschritte der Wissenschaft uns mit Stoffen bekannt machten, welche das Vermögen einer hohen bacteriziden Fähigkeit besaßen, ohne die den bisherigen Antiseptis anhaftenden Schädigungen der Gewebe. Es sind dies die auf dem Wege der Autolyse aus Bakterien gewonnenen bakteriziden Substanzen, auf deren Vorkommen und Bedeutung zuerst Emmerich und Low die Aufmerksamkeit gelenkt haben."

² The resumption of these endeavours first became possible when the march of science made known to us substances which possessed a high bactericidal capacity without at the same time harming the tissues as do previously known antiseptics. These are the bactericidal substances obtained from the autolysis of bacteria, the existence and significance of which Emmerich and Low first drew attention.

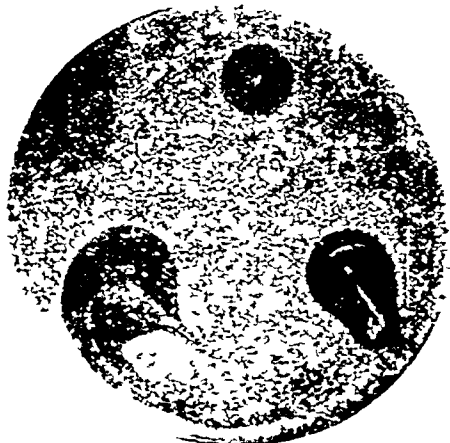
It is interesting to note that as recently as 1943 Rake, Jones & McKee found that a good preparation of pyocyanase inhibited the growth of *Str. pyogenes* at a dilution of 1 in 24,000. Recently Doisy and his colleagues (Hays, Wells, Katzman, Cain, Jacobs, Thayer, Doisy, Gaby, Roberts, Muir, Carroll, Jones & Wade, 1945) have isolated from the products of *Ps. pyocyanea* four crystalline substances, Pyo I, II, III, and IV, which act powerfully against gram-positive organisms and appear to have little toxicity to animal tissues.

Antibiotics from a Micrococcus and from Aerobic Sporing Bacilli

While these clinical trials were being made, other investigations were being recorded. In 1903 Lode wrote of an accidental contaminant, a gram-positive coccus, which he had found while preparing a plate of *Micrococcus tetragenus* for class demonstration (Fig 4). He subcultured this organism and showed that it produced a diffusible substance which strongly inhibited the growth of anthrax bacilli and *Staph. aureus*, but not *Bact. coli* or Friedlander's bacillus. Lode did comprehensive and painstaking investigations of this substance. He showed that it was bactericidal, and that it was not an enzyme, though it was thermolabile, being inactivated slowly by heat. It could be dried by vacuum distillation and was soluble in alcohol but not in ether. Neither the micro-organism nor its metabolic products were toxic to animals, but unfortunately in artificially produced infections in mice the product had no chemotherapeutic effect.

In 1907 a Frenchman, Nicolle, demonstrated the existence of bactericidal substances produced by a common spore-

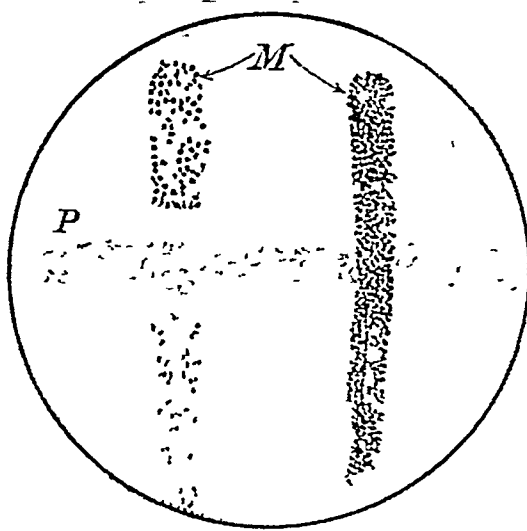
FIG 4. ONE OF THE FIRST BACTERIAL ANTAGONISMS STUDIED (Lode, 1903)



Lode noticed that a culture of *Micrococcus tetragenus* was inhibited by an accidental contaminant—a coccus. He isolated this coccus and studied its antagonistic properties extensively. He found that some kinds of bacteria were inhibited more than others and some not at all (differential action) that the number of bacteria to be inhibited affected the efficiency of the antagonist (inoculum size effect) and that the antagonist was bactericidal. He succeeded in obtaining the active material in fluid culture and made observations on the conditions necessary for its production and on its chemical nature.

The gelatin plate illustrated was sown with *M. tetragenus* which was inhibited round the three colonies of the coccus.

FIG 5. INHIBITION BY PNEUMOCOCCUS OF MENINGOCOCCUS (Colebrook, 1915)

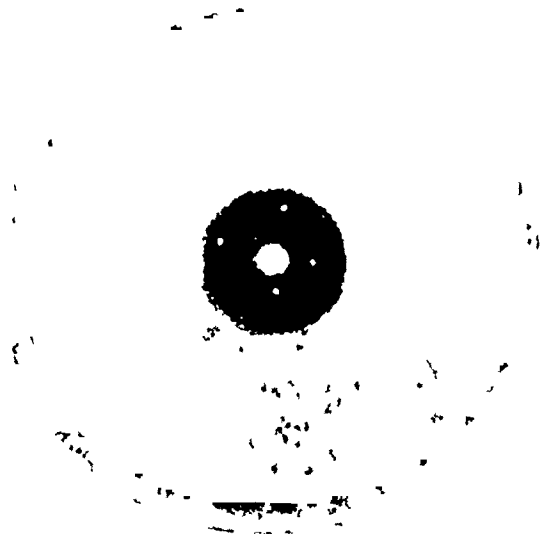


Colebrook noticed that the pneumococcus inhibited many other bacteria in culture. His illustration shows a streak of the pneumococcus (horizontal) crossed by two streaks of meningococcus (vertical). The pneumococcus inhibited the left-hand streak which was made by inoculating a relatively small number of meningococci but had no effect on the right hand streak where the inoculum was heavier. Most antiseptic substances are subject in some degree to this 'inoculum size effect', and if the effect is great the therapeutic value of the substance is thereby reduced. Colebrook attempted to use the antibiotic properties of the pneumococcus by spraying it into the throats of carriers of the meningococcus in the hope that it would establish itself and replace the meningococcus.

forming soil bacterium known as *Bacillus subtilis*. At about the same time, in France, Rappin experimented upon the effects of filtrates of the spore-forming *B. subtilis*, *B. mesentericus*, and *B. megatherium* on the tubercle bacillus. He wrote in 1912:

'Après avoir constaté, il y a déjà longtemps, l'action si énergique de ces diastases, je fus naturellement amené à penser que, peut-être, elles étaient susceptibles aussi de posséder des propriétés importantes sur l'évolution de la tuberculose et il y a près de deux ans, j'instituai quelques expériences dans le but de vérifier cette hypothèse. J'injectai ainsi à quelques cobayes préalablement inoculés de tuberculose des cultures filtrées de *B. mesentericus* et je possède encore aujourd'hui un animal de cette première série qui, traité de la sorte, conserve plus de vingt et un mois après l'inoculation virulente toutes les apparences d'une parfaite santé. Un autre qui mourut au bout de neuf mois, sans avoir manifesté aucun trouble et après avoir suivi une ascension régulière de son poids ne présentait aucune lésion à l'autopsie: on notait seulement l'existence d'un ganglion à l'inoculation et un autre de l'autre côté. Enfin fait très important, le produit de raclage de ces ganglions inoculé à un autre animal n'a paru déterminer jusqu'ici chez ce dernier aucune réaction.

'Répétée sur d'autres cobayes cette expérience a donné des résultats semblables et je possède plusieurs animaux

FIG. 6. INHIBITION OF ONE STRAIN OF BACT COLI BY ANOTHER (Gratia, 1925)

The agar plate was sown all over with one strain of *Bact coli*, and the other strain, which produced an inhibitor, was planted in the centre. After incubation a zone of inhibition was seen round the central colony, though four isolated colonies had grown within the zone. It is not uncommon for a few resistant bacteria to grow from a strain otherwise sensitive to an antibiotic and this may complicate testing, particularly in liquid media.

traités de la sorte à des époques plus ou moins éloignées de l'inoculation tuberculeuse qui demeurent en pleine santé apparente, alors que leurs témoins sont morts présentant toutes les lésions classiques de la tuberculose expérimentale.

"Pour obtenir ces résultats, un nombre relativement faible d'injections a suffi. Quelques-uns de ces animaux ont reçu seulement deux injections de bouillon filtré de *mesentericus* à la dose de un à deux centimètres cubes sous la peau et d'autres la même quantité mais dans la cavité péritonéale, sans que ni les uns ni les autres n'aient du reste paru touchés par ces injections, ni présenté de réactions."

Zukerman & Minkewitsch (1925) found on a plate of pseudo-diphtheria bacilli an accidental contaminant antagonistic to their growth. The organism was *B. mesentericus vulgaris*, and it showed antagonism only to diphtheria and pseudo-diphtheria bacilli, not to staphylococci, *Bact coli*, *Bact typhosum*, or a number of dysentery bacilli. Also in 1925 Rosenthal contributed work on the bacteriolytic powers of *B. scaber*, another spore-forming organism. Some of the more recent work with spore-forming organisms will be referred to later.

Bacterial Substitution Therapy

There were various attempts after Cantani's to replace harmful by harmless bacteria. Schiøtz (1909), a Danish physician, noticed that a patient with a staphylococcal infection, wrongly diagnosed as having diphtheria and placed in a diphtheria ward, did not develop the disease. Schiøtz then deliberately sprayed suspensions of staphylococci into the throats of carriers with, he claimed, good results. The best-known attempt at such "replacement therapy" was that suggested by Metchnikoff (1909), to replace what he considered harmful organisms in the intestine by the Bulgarian lacto-bacillus, later workers used a similar organism, *B. acidophilus*, in the same way. In 1915 Newman treated

cases of cystitis by injecting lactic acid bacilli into the bladder, in the same year Colebrook showed inhibition of meningococci by pneumococci (Fig 5), and suggested using the pneumococcus to combat the meningococcus in the throats of carriers, and in the following year Nissle (1916), maintaining that certain strains of *Bact coli* were antagonistic to other, more harmful organisms, put on the market a product called "mutaflor", a preparation of living *Bact coli* which were supposed to replace these more harmful organisms in many intestinal diseases. A similar antagonism was described in 1925 by Gratia, who published an illustration demonstrating the inhibition of one strain of *Bact coli* by another (Fig 6). In the same year Alivisatos showed the inhibition of staphylococci by pneumococci (1925, Fig. 7). The pneumobacillus of Friedlander was suggested by Papacostas and Gate (Papacostas & Gate, 1921, Gate & Papacostas, 1921) for the treatment of diphtheria carriers.

In connexion with the idea of "fighting" one bacterium with another, an interesting line of reasoning was displayed by a Pole, Nitsch (1908), who was in France at a time when the towns of Lyons and Versailles were notorious for their freedom from epidemics of cholera. It occurred to him that possibly bacteria in the air of these regions might have the property of inhibiting the growth of the cholera organism, and that if they were swallowed they might exert their antagonistic effects in the intestine. He found eleven strains of air bacteria out of 220 from various parts of Versailles, and four out of 253 from Paris, which when cultured at

FIG 7. INHIBITION OF STAPHYLOCOCCUS BY PNEUMOCOCCUS (Alivisatos, 1925)

The culture plate was sown with a suitable mixture of pneumococcus and staphylococcus. After incubation, clear zones where the staphylococcus had not grown were seen round the colonies of pneumococcus. Alivisatos tried to show whether the inhibition was caused by a chemical metabolite by growing the pneumococcus in ascites broth and spreading the broth, after sterilizing it by filtration, on a plate sown with staphylococci, but the result of this experiment was negative. He showed that many strains of pneumococcus had inhibitory power.

37° C inhibited the growth of *Vibrio cholerae*. Another Pole, Choukevitch, in 1911 continued these observations, with three of Nitsch's Versailles strains of cocci. He confirmed that if a streak of one of these organisms was planted on an agar surface and *V. cholerae* was planted at the same hour on the following day, growth of the vibrios did not take place within a distance of 1 cm from the antagonist. He found that the inhibition was not due to acid, that the inhibitory substance developed in broth as well as in solid media, and that it was thermolabile and not capable of filtration. He attempted to establish the cocci in the intestines of new-born rabbits, but was not able to demonstrate any protection against ingested cholera organisms.

Other Ideas for Use and Production

In 1917, in Australia, Greig-Smith made the first observations on the actinomycetes; he noticed that some of these organisms grown from soil had the power of stopping the growth of certain bacteria. In 1921 Lieske published a monograph on the subject of antibiotics produced by actinomycetes and there were important contributions soon afterwards by Gratia & Dath (1924, 1925), who examined many sources for organisms producing antagonistic substances, and were particularly struck by the effects of a streptothrix which caused the dissolution of the staphylococci with which the plate was heavily sown (Gratia, 1934, Fig 8). They used the lytic powers of the substance produced by their streptothrix or actinomycete instead of heat to kill the bacteria used in the preparation of vaccines known as mycolysates. Kimmelstiel, Much and Sartorius (Kimmelstiel, 1923, 1924, Much, 1925, Much & Sartorius, 1924, Sartorius, 1924) made similar attempts to use bacteria dissolved by ferments produced by micro organisms; their product was sold under the name of "sentocym". More recent work on *Actinomyces* will be referred to later.

In the nineteen-twenties a new idea, which has yet to be developed, was introduced by Schiller (1924a, 1924b, 1925a,

FIG 8 INHIBITION BY A STREPTOTHRIX (Gratia, 1934)



Gratia showed that some strains of streptothrix had the power to dissolve bacteria. A heavy emulsion of staphylococci was incorporated in a gelatin culture plate and the streptothrix was planted on the surface (A and isolated colonies). After 3 days as the illustration shows the staphylococci near the streptothrix had dissolved and in a week the medium had cleared completely. Gratia made use of a streptothrix to dissolve bacteria for vaccines and the mycolysates as he called them were used clinically.

FIG 9 INHIBITION OF ONE MOULD BY ANOTHER (Harder, 1911)



Harder a botanist published in 1911 an account of inhibitions which he had observed among Basidiomycetes and Ascomycetes growing in culture. This illustration from his paper shows a colony of *Penicillium luteum* (above) stopping at a distance the spread of *Stereum purpureum* (below) over the culture plate.

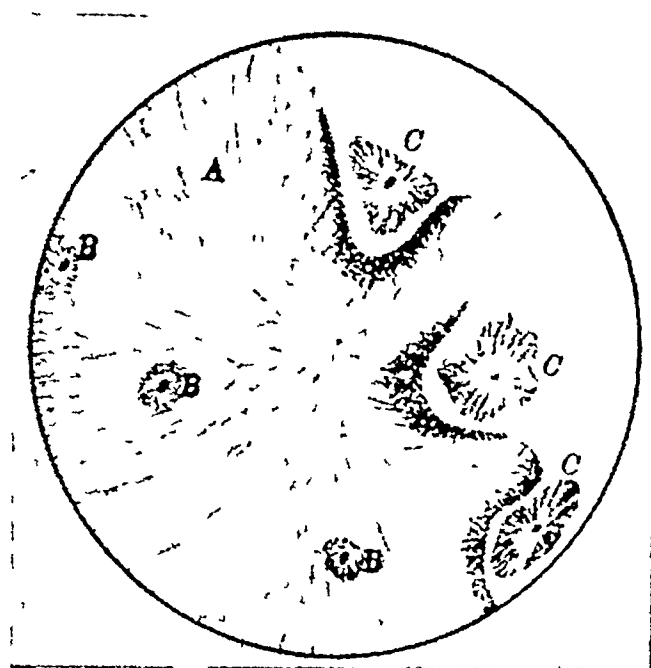
1925b, 1927, Schiller & Giltcher, 1928). He brought forward evidence that yeasts and possibly other organisms could be trained to produce substances that were antagonistic to certain bacteria, by growing them on media in which the only source of nitrogen was the bodies of the bacteria it was desired to antagonize. He claimed that in such experiments yeasts developed a thermolabile inhibitory substance which might be of value in therapeutics. He called the phenomenon "induced" antagonism, in contradistinction to the "natural" antagonisms.

Mould Products

The first example of a mould yielding an antibiotic was recorded in 1896 by Gosio, when he obtained a crystalline substance from a *Penicillium* in the course of his investigations on mouldy maize, thought at that time to be the cause of pellagra. The antibiotic is now called mycophenolic acid. Gosio showed that the crystalline material inhibited the growth of anthrax bacilli, and regretted that he was unable to perform animal experiments because of lack of material. Recently the antibiotic and biological properties of this substance have been more fully investigated (Florey, Gilliver, Jennings & Sanders, 1946). Vaudremer found that the mould *Aspergillus fumigatus* would digest "the tubercle bacillus, though he had a dispute with Rappin over the question of priority. In 1913 Vaudremer reported animal experiments, and described in the following terms the results of injecting *A. fumigatus* filtrates into patients suffering from tuberculosis.

"Toute conclusion est également prematuree si on envisage le traitement de la tuberculose humaine. Depuis 1910, nous avons traite plus de deux cents malades avec les extraits

FIG 10 PRODUCTION OF AN ANTIBIOTIC BY ONE SPECIES OF *PENICILLIUM* BUT NOT BY ANOTHER (Porter, 1924)



Porter, a botanist, tried to protect plants from attack by fungi, by using the antibiotic properties of bacteria or of other fungi. He tried both growing the inhibitory organism near the plant it was desired to protect, and also injecting its metabolic products, e.g. into an orange exposed to the spores of a mould. His illustration shows that one species of *Penicillium* (C) inhibited at a distance the growth of *Pestalozzia* (A), while another species of *Penicillium* (B) had no effect.

d'*A. fumigatus*, le traitement a été appliqué dans plusieurs hôpitaux et sanatoriums parisiens. Des faits que nous avons observés, on peut conclure à l'innocuité de ces injections qui ne provoquent jamais de réaction fébrile. Parfois même on voit survenir des guérisons inespérées. Dans d'autres cas, on observe une amélioration passagère, mais malheureusement les faits sont encore nombreux où la tuberculose poursuit son évolution."

Vaudremer had been trying to get a direct effect on the tubercle bacillus *in vivo* by injecting a mould metabolism solution. It is now known that *A. fumigatus* produces four antibiotic substances, at least one of which, helvolic acid (Cham, Florey, Jennings & Williams, 1943; Waksman & Geiger, 1944) has some action against the tubercle bacillus *in vitro* (Jennings, 1945).

Meanwhile, during this quarter-century of sporadic development, important methods and observations had been elaborated by botanists. Reinhardt, for example, in 1892, had described the inhibition of a fungus, *Peziza trifolium*, by a bacterium at a distance of 25 mm, as well as antagonisms between *Penicillia* and *Aspergilli* when these were grown on solid media. In 1911 Harder showed the inhibition of *Stereum purpureum* by *Penicillium luteum* (Fig 9). Many observations were made and general technical procedures furnished by Porter (1924), who noted, among other things, that a penicillium inhibited the growth of *Pestalozzia* (Fig 10). An interesting example of fungal inhibition, using the technique of growth on agar, was described by Nadson & Jolkevitch (1923), who found a contaminating fungus, which

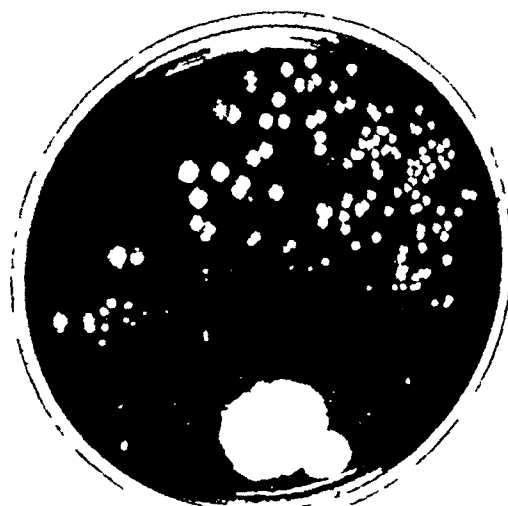
they later called *Spicaria purpurogenes*, with the capacity to kill the common baker's yeast.

The observation on the moulds which has had most consequence was made in 1929, when Fleming noticed a mould which had accidentally fallen on to one of his culture plates and which was causing the dissolution of staphylococci in its neighbourhood (Fig 11). He subcultured this mould (subsequently identified as *Penicillium notatum*) in broth and found that it secreted something into the broth which had the power of stopping the growth and eventually slowly killing many pathogenic organisms. He called the broth in which this antibacterial substance had been secreted penicillin, and later the antibacterial substance itself was given this name. He observed that the broth acted on many important pathogenic organisms such as the streptococcus and staphylococcus, while others, such as *H. influenzae* and the *Salmonellas*, remained unaffected. The crude metabolism liquid was shown not to be more toxic to animals than broth in which nothing had grown. No curative experiments were performed on experimental infection in animals, but the suggestion was made that the substance would be useful for dressing septic lesions in man, and indeed some were so treated without, however, any very striking results. The clinical possibilities of this antibiotic were not pursued until the beginning of the next decade, although Fleming maintained his strain of the mould and made use of the broth in differential culture media in the laboratory.

The Position in 1939

The position at the end of the nineteen-thirties may perhaps be summarized thus. A very large number of observations on antibiosis had been recorded from 1877 onwards—some of the most striking have been considered, but there were a great many more—and from all this work

FIG 11 THE FIRST OBSERVATION ON *PENICILLIUM NOTATUM* (Fleming, 1929)



This is a photograph of the original plate on which Fleming found a colony of *Penicillium* dissolving the surrounding colonies of staphylococci. Not all bacteria were susceptible to the action of the mould, and Fleming made use of this property by incorporating the broth on which the mould had grown in media for differential culture. Among other experiments he showed that the broth was more toxic to bacteria than to human leucocytes *in vitro*.

certain proposals had emerged for the use of micro-organisms in therapeutics

1 The replacement of a pathogenic organism by another and less harmful organism—for example, "*Bact termo*" to replace the tubercle bacillus in the lungs, staphylococci to replace diphtheria bacilli, and pneumococci to replace meningococci, in the throat, lactic acid bacilli and *Bact coli* to replace organisms infecting the intestine

2 Artificial immunization by one organism to protect against infection by another

3 The use of lytic substances from one organism for the preparation of soluble vaccines of other species—for example, Much's sentocym and Gratia's mycolysates

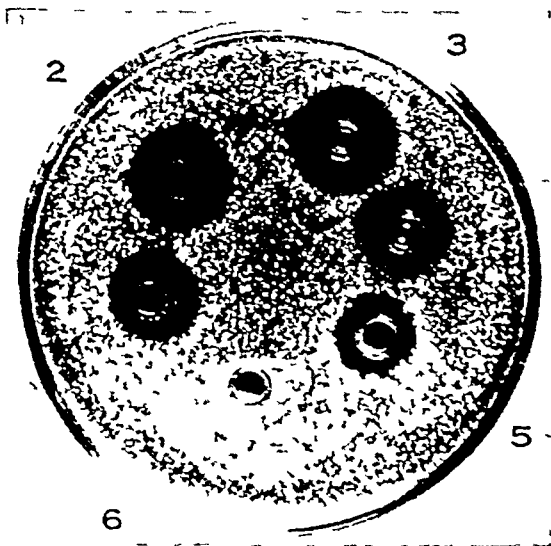
4 The use of soluble bacterial or mould products as a topical application for the treatment of local infections—for example, pyocyanase and penicillin broth

5 The use of soluble bacterial or mould products by parenteral injection to treat established diseases—for example, pyocyanase in anthrax, and Vaudremer's extracts of *Aspergillus fumigatus* and Rappin's extracts of *B subtilis* in tuberculosis. These were examples of true chemotherapeutic use

Discovery of Penicillin's Chemotherapeutic Powers

In the early part of 1939 a wide investigation of natural antibacterial substances was planned by Dr Chain and myself, and penicillin was one of the first chosen for investigation. In 1932 Clutterbuck, Lovell & Raistrick had published

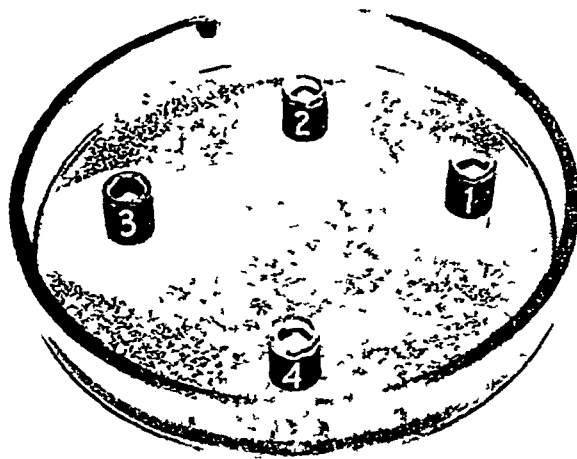
FIG 12. ACTIVITY OF LICHENS AGAINST BACTERIA (Burkholder, Evans, McVeigh & Thornton, 1944)



Extracts of lichens were made in a mortar and tested by the cylinder-plate method against various bacteria. In the experiment illustrated the lichens were extracted by grinding them with ether, the ether was then evaporated and the residue taken up in buffer pH 7.4 for testing. This is a useful method for testing for the presence of antibiotics which are insoluble in water but can be extracted by an organic solvent.

The bacterium on the plate is *B. cereus* and the numbered cylinders contain extracts of *Cladonia cristatella* (2), *C. caroliniana* (3), *C. Grayi* (5) and *C. coniocraea* (6).

FIG 13. INHIBITION BY GREEN PLANTS (Osborn, 1945)



Plants have from prehistoric times been used for medicines and some have had a high reputation for preventing suppuration in wounds. Certainly many plants can be shown to contain antibacterial substances. The cylinders on the plate illustrated contain watery extracts of

- 1 *Allium sativum*
- 2 *Spiraea aruncus*
- 3 *Ranunculus bulbosus*
- 4 *Prunella vulgaris*

The last, which was negative in this test, was called 'self heal' and was recommended by 17th century herbals for treating wounds

a paper in which they showed that penicillin could be produced by the mould on a synthetic medium, and that it could be extracted from water into ether if the water was made acid, but that large losses of antibacterial activity occurred on the evaporation of the ether. They had recognized that penicillin was most stable around neutrality, but had stated that it was a very labile substance, and they did not carry the work further. Based on this work we found, with our colleagues at Oxford, a method for extracting the penicillin and making preparations which, though crude, had high antibacterial activity. After some preliminary biological experiments with these extracts, it became clear that the substance might be of exceptional interest and a team of workers was assembled in the Sir William Dunn School of Pathology at Oxford. In 1940 the first observations on penicillin from Oxford were published (Chain, Florey, Gardner, Heatley, Jennings, Orr-Ewing & Sanders), which clearly distinguished this antibiotic from any of its predecessors. They showed that artificial infections in mice with the streptococcus, staphylococcus and *Cl. septicum* could be completely controlled by injections of a penicillin extract, so that there was almost 100% survival from infections which would otherwise certainly have been fatal. In other words, penicillin was a chemotherapeutic drug of great power, that is to say, it was of such low toxicity that it could, without producing any toxic signs, be injected by parenteral routes in amounts which would stop the growth of bacteria in all parts of the body. Many other investigations were made. A full account of these, together with the results of the first clinical trials, was published in 1941 (Abraham, Chain, Fletcher, Florey, Gardner, Heatley & Jennings) and the results of a larger clinical trial in 1943 (Florey & Florey). Two of the facts of

especial importance which emerged from the laboratory work at Oxford were, firstly, that extracted penicillin was fully active in the presence of pus and tissue-breakdown products, and of large numbers of bacteria, all of which impaired the antibacterial action of all the sulphonamides known at that time, and, secondly, that even very impure extracts were non-toxic to animals in concentrations hundreds of times greater than those required to inhibit bacteria, and that with increasing purity of the extracts the toxicity became still less (Florey & Jennings, 1942)

Examples of Recent Work on Some Special Groups

Sporing Aerobic Bacilli

At the present time a widespread survey of natural sources, such as plants, moulds, and bacteria, is being made for the presence of antibiotics. In 1939 Dubos, after long study and preparation of soil bacteria, had described the isolation of a powerful selective antibiotic from a spore-forming soil bacillus, *B. brevis*. In collaboration with others he investigated this substance, now known as tyrothricin, from both a chemical and biological point of view, and in the clinic Tyrothricin was found to consist of two crystalline polypeptides, gramicidin and tyrocidine, which are both antibiotics. They have proved too toxic to act as chemotherapeutic agents, but have had some use as local applications, and have proved to be of the greatest interest to the crystallographers for the study of protein structure by x-ray methods. Gramicidin was shown to be particularly active against gram-positive organisms such as pneumococci and streptococci.

From the group of spore-forming bacteria, also, Johnson and his collaborators (Johnson, Anker & Meleney, 1945) have prepared a substance which they have named "bacitracin". This seems to affect the same range of bacteria as penicillin, it has been shown capable of controlling experimental disease in mice, and can be used successfully at least as a surface application for disease in man.

This group of organisms is the subject of active research at the present time in more than one country, and new publications continue to appear.

Actinomycetes

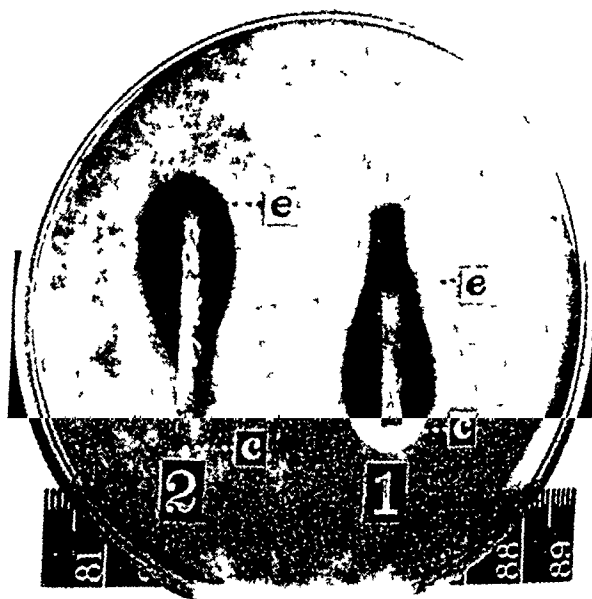
Among several antibiotic substances extracted by Waksman and his colleagues (Schatz, Bugie & Waksman, 1944) from the actinomycetes, one known as streptomycin has been investigated which has proved to be particularly interesting. Although little toxic to animal tissues, it stops the growth of many pathogenic organisms at high dilution, and is active against some of the organisms not inhibited by penicillin, for instance, some of the gram-negative organisms such as *Bact. coli* and *Ps. pyocyanea*, and it has some effect against the tubercle bacillus. Its possible use for the treatment of tuberculosis is now being actively pursued, but it is still too early to say what it may achieve. Waksman & Woodruff (1942) have also described streptothricin, a substance similar to, but more toxic than, streptomycin, and Gardner & Chain (1942) isolated, from an accidental contaminant, proactinomycin, which acts against gram-positive organisms, and has been shown to have chemotherapeutic properties against peritoneal infection by the streptococcus when given by mouth (Florey, Jennings & Sanders, 1945). Its range of antibacterial activity is very similar to that of

penicillin, but it is probably too toxic to be used in man, and such great progress has been made in chemotherapy during the last few years that it is now of little interest except to add to the list of naturally-produced antibacterial substances with chemotherapeutic properties.

Higher Plants

Higher forms of plant life also contain antibacterial substances. Burkholder and his colleagues (Burkholder, Evans, McVeigh & Thornton, 1944) examined a large number of lichens, which are a symbiosis of fungus and alga, by grinding them up with saline or other solutions and testing the liquid extract, and found that many contained inhibitory substances (Fig 12), some of which it was suggested might be lichen acids, but as yet no real chemical examinations are reported and no further biological examinations. In a

FIG 14 METHOD OF TESTING THE ANTIBACTERIAL POWER OF BASIDIOMYCETES AND OTHER FUNGI DIFFICULT TO GROW IN LIQUID CULTURE (Wilkins & Harris, 1944b)



The fungus to be tested was grown on a solid medium and when the colony was well developed radial strips were cut out of it and removed, together with the underlying agar. Warm agar was sown with a test organism such as a staphylococcus, and poured into a Petri dish. Before the agar set, the strips from the fungus colony were dropped into it. The plate was then incubated. The illustration shows inhibition by two species of Basidiomycete *Tricholoma nudum* (1) and *Clitocybe aurantiaca* (2). In the former the older part of the fungus colony (c) has produced the most inhibitor, while in the latter the younger part (e) has produced the most.

similar way upwards of three thousand green plants have been examined by Osborn (1943, 1945, Fig 13), and by others (for example, Cavallito, Buck & Suter, 1944, Cavallito, Bailey & Kirchner, 1945), with the discovery of many with an antibacterial action.

Heatley, in investigating (1944) the antibiotic produced by a small wild flower, *Crepis taraxacifolia*, elucidated an interesting phenomenon. He found that an inactive precursor was present in the plant and that the yellow petals of the flower contained an enzyme which, by acting on the precursor, produced the antibiotic. This he crystallized and

called crepin. As an antibacterial substance it is of little interest, although it has a powerful pharmacological action on the mammalian heart, but it is interesting to speculate in what way, if any, this enzyme-substrate reaction can benefit the plant, and whether its antibacterial powers have any significance.

From the surveys which have been made of scientific collections of fungi and of higher plants, as well as from the examination of stray contaminants, one sees that literally hundreds of producers of antibacterial substances are now known and that probably hundreds of new compounds await a comprehensive investigation.

Possible Further Uses of Antibiotics

Antibacterial action, however, is only one aspect of the potentialities of these substances, for their possible effects on protozoa and other non-bacterial causes of disease, particularly in the tropics, and on the fungi which cause skin infections, are as yet little explored. In this connexion there is interest in a substance which, it now appears, was first detected by Dutch workers (van Luyk, 1938) in the course of an investigation of *Penicillium expansum*. They eventually extracted a crystalline antibiotic which they called expansine, the same as that which has later been obtained from several other moulds and goes under a variety of names—clavacin, clavatin, claviformin, patulin, penicidin. This substance has a powerful antifungal effect and was used by the Dutch observers for treating fungus diseases of the skin. Sanders (1946) has found that many pathogenic fungi are inhibited by it at a dilution of at least 1 in 160,000, but it is toxic even when applied locally and its possible place in therapeutics remains to be seen. Both gramicidin and penicillin have been used in veterinary medicine, and the interest of antibiotics is not confined to human or animal therapeutics, for penicillin has been used successfully and apparently economically to treat the galls on apple trees caused by a susceptible bacterium, by injecting crude metabolism liquor containing penicillin into each gall (Brown & Boyle, 1944), and other bacteria and some of the fungi which cause plant diseases have been shown to be susceptible to antibiotics (Waksman & Bugie, 1943; Anslow, Raistrick & Smith, 1943; Gilliver, 1946).

Procedure of Antibiotic Research

The procedure for investigating substances which may be antibiotics is now fairly clearly established, and should be systematically followed. First the production of an antibacterial substance must be demonstrated. Usually moulds and bacteria are grown in liquid media and the liquid is examined by some such method as Heatley's cylinder-agar plate technique for inhibition of staphylococcus, *Bact. coli* or other selected organisms. This method of testing is equally suitable for testing any liquid extract and has been applied to the examination of plants and other possible natural sources.

Many basidiomycetes have been shown by Wilkins & Harris (1944a, Wilkins, 1945) to produce antibacterial substances, and as most of these fungi grow very slowly in artificial culture and do not produce spores, the initial detection of their antibacterial action presents some difficulties. Wilkins and Harris grew the fungus on a solid medium and then with a sharp tool cut out a section passing through the centre of the colony. This section was embedded in an agar plate sown with bacteria, and if inhibitors were present they

diffused out and inhibited the bacteria in the plate. It was possible by this means to see whether the younger or older part of the fungus produced the antibiotic (Wilkins & Harris 1944b, Fig. 14).

After it is demonstrated that an antibiotic is present, the first step towards the investigation of any substance is to find the best conditions for its production. In the case of fungi and bacteria it is a matter of finding the best cultural conditions and the best composition of the culture medium. With fungi in particular, the latter is often of the greatest importance, for a fungus may grow luxuriously and yet produce no antibiotic if the medium is not suitable, whereas on another medium, on which growth may be poorer, the antibiotic will be produced. With plants the production of the antibiotic has to be considered in relation to the season of the year, the phase of growth of the plant, the different parts of the plant, and so on. Then comes the examination of the best way to extract the substance. Though each extraction presents a new problem, experience has shown that certain lines of investigation should be followed. Many substances are soluble in organic solvents and most of these are relatively easy to purify, especially by means of chromatography. Neutral substances which are insoluble in organic solvents, however, still offer great difficulties in purification, but gradually methods are being evolved to deal with substances of this class.

After the substance has been extracted in a highly concentrated or pure form, the range of organisms against which it is active—usually pathogenic organisms are considered first—is determined, together with such data as whether it is inactivated by serum or body-fluids. The toxicity to whole animals, usually mice, is determined, and it is particularly important to determine the effect of repeated injections, for in chemotherapeutic practice repeated doses will always be necessary. For example, some antibiotics, of which a single injection is well tolerated, produce liver damage when the injection is repeated often. Toxicity to individual tissues is determined by *in vitro* observations on leucocytes or tissue cultures and by injections into the cerebrospinal cavity or other selected sites in animals. Pharmacological investigations into the effect of the substance on the most important physiological functions follow. Of these, the observations on the heart, blood pressure and respiration are the most important. If, at the end of these investigations, a substance appears to be both sufficiently powerful against bacteria and sufficiently non-toxic, protection experiments on appropriate animals, such as mice, or, for the tubercle bacillus, guinea-pigs, become justifiable. The infection must, of course, be induced by an organism sensitive *in vitro* to the antibiotic under test, and in order to determine the route and frequency of administration, and the size of the dose, studies on absorption and excretion in animals must be carried out.

The failure to carry out systematically this scheme of procedure undoubtedly accounts for the publication of many investigations which are far from complete. In any case, before serious trials on man are carried out, comprehensive laboratory work is necessary. One lesson has, I think, been clearly learnt of very recent years—that, in the field of antibiotic research, continuous and satisfactory progress can be expected only when people with different technical attainments and different outlooks agree to combine for comprehensive investigations. Few individuals have the knowledge and technical accomplishments to carry through all the necessary chemical and biological investigations completely.

The skilled investigation of the chemistry of such substances may lead to a better understanding of antibacterial action. The antibiotics so far known are mostly complex substances of large molecular weight, and the structure of few of them has so far been elucidated. As Dubos has insisted, much biochemical interest attaches to the clarification of the mechanism by which these substances produce their effects, for a thorough knowledge of this may bring with it the ability

to construct, as it were, tailor-made chemotherapeutic agents suitable for every infection. From a still wider point of view the clear definition of these antibacterial substances may help us to understand the ceaseless struggle for existence which is being continually waged by microscopic organisms everywhere.

Fig 1, 2, 3, 4, 6, 8 and 11 are reproduced from blocks kindly lent by the Editor of the *British Medical Journal*.

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ANALYSIS OF ANTIBACTERIAL ACTION

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Recovery of a host from infection implies that the conflicting interests of two species—host and parasite—have in the instance concerned been decided in favour of the host. We are at present interested in cases in which the recovery has been favoured by administration of substances to the already-infected host, and, in particular, in those cases in which the action of the chemotherapeutic agent concerned (or of a substance derived from it in the host) is upon the parasite. These instances include the majority of well-established chemotherapeutic actions, but it will be realized that the class of antibacterial agents is much more extensive than is the class of chemotherapeutic agents which affect bacteria. It includes many inhibitory substances whose behaviour in a host would make them unsuitable for chemotherapy. In order, however, to develop the study of antibacterial agents to a point at which it may be useful in chemotherapy, it will be advantageous not to emphasize the chemotherapeutic efficacy of the agents studied. The question of whether chemotherapeutic agents show any particular type of antibacterial activity can then be raised at a later point.

TYPES OF ANTIBACTERIAL ACTION

Growth of the parasite at the expense of the host is an essential part of infection and leads to the choice of growth and viability as criteria in classifying antibacterial effects into the following three types

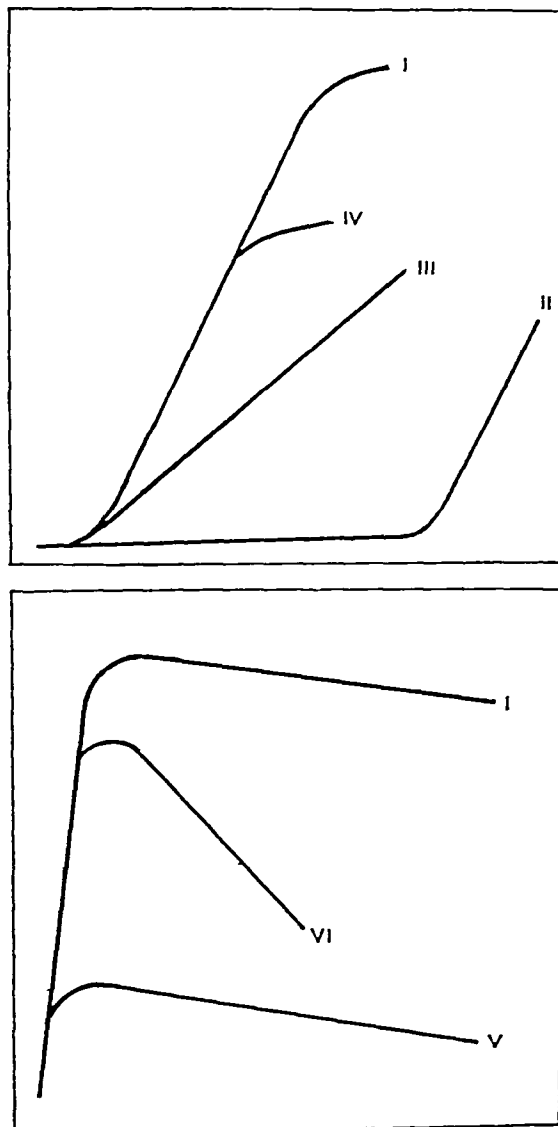
A. Actions on Bacterial Products, without much Effect on Growth and Viability

Such action becomes of interest to chemotherapy when the products affected are of types which are concerned in the relation between parasite and host, of these, the most important are antigenic substances, toxic to the host or protective to the organism. The use of antitoxins constitutes an important part of chemotherapy, but one which is conventionally studied apart from it. Of agents affecting protective substances, Dubos' findings (1939-40) are outstanding. By presenting a pneumococcal capsular polysaccharide as main nutrient to soil bacteria, a species was isolated which yielded an enzyme capable of breaking down specifically that polysaccharide, *in vitro* and *in vivo*. Growth of the pneumococci was otherwise normal *in vitro*, but *in vivo* the non-capsulated cells underwent phagocytosis and were unable to cause infection which proceeded in the absence of the enzyme. In this case the action of the agent was such as to afford an immediate experimental connexion with a specific constituent of the bacterial cell, of known function. This makes its action readily understandable, as will be seen below, much investigation is required before such knowledge of other types of agent is attainable.

B Effects upon Growth

Effects on growth are many and some description must precede attempts at their understanding. If initial observations are confined to the increase of bacterial substance during growth of cultures, ignoring the morphology of the cells so produced, the growth-curve becomes the basis of description. Curve 1, Fig 1, represents the course of growth commonly found in an uninhibited culture, and the effects which different agents have been observed to have upon such growth include the following: Increase in lag

FIG 1 and 2. DIAGRAMS REPRESENTING THE COURSE OF GROWTH OF BACTERIAL CULTURES



Abscissae = time
Ordinates = logarithms of numbers of organisms
Fig 2 covers a longer period of time than Fig 1
Curve I in each represents normal growth the other curves represent cultures under the influence of various substances which are referred to in the text.

(as in curve ii) is the principal effect of sublethal concentrations of proflavine and methylene blue on *Bact. lactis aerogenes* (Davies, Hinshelwood & Pryce, 1944). Decrease in rate of growth (curve iii) is the first action produced on growth by sulphonamides (Kohn & Harris, 1941) and pantoyletaurine (McIlwain, 1944), and also one of the effects of concentrations of phenol, mercuric chloride, cupric salts and formaldehyde lower than those which are bactericidal (Poole & Hinshelwood, 1940). Limitation of stationary population (curve iv) is also caused by sublethal concentrations of phenol, HgCl_2 , Cu^{++} , and formaldehyde, but the present effect can be shown to be secondary to the action on growth-rate (Poole & Hinshelwood, 1940). Adverse pH can lower stationary population with little effect on growth-rate.

C Effects upon Viability

If investigation of the numbers of organisms in normal cultures is continued beyond their "stationary" population, as in Fig. 2, it is found that a slow death-rate ensues (curve i). A proportion of organisms is, in fact, dying even during the growth of the culture as a whole. This can become apparent during the action of a bacteriostatic compound, as in curve v. In addition, some compounds regarded as primarily bacteriostatic—such as the sulphonamides—may to some extent accelerate this process (Wolff & Julius, 1939; Colebrook & Cawston, 1945), but the agents termed bactericidal impose a much greater death-rate upon the culture, such as that represented by curve vi.

Until recently it did not appear that bactericidal agents were of great chemotherapeutic interest because their toxic action tended to show little specificity and to extend to animal tissues. Their potentiality has, however, been shown by penicillin, though the action of this substance is not one which has been regarded as typical of bactericidal agents. Phenol or formaldehyde can show differences in the intensity of their action upon bacteria at various stages of their growth, but with penicillin such differences become extreme. Penicillin had little action on staphylococci, streptococci or meningococci whose growth was prevented by lack of nutrients, or, when nutrients were provided, by boric acid or by cooling. But under conditions which normally allowed bacterial growth, as in ordinary broth or serum, penicillin caused their death (Bigger, 1944; Hobby & Dawson, 1944; Miller & Foster, 1944; Hirsch, 1943-44). A further peculiarity of the action of penicillin on staphylococci appeared to be connected with its failure to act on non-proliferating organisms. This was the non-susceptibility to penicillin of a very small proportion of individuals in staphylococcal cultures. When, later, such organisms were caused to grow, they were of normal susceptibility to penicillin.

Bactericide by penicillin requires a definite period of exposure of organisms to the drug, and this period increases with decreasing concentrations of penicillin. Bactericidal effects initiated by penicillin could result in the death of organisms after their removal from penicillin-containing media (Parker & Marsh, 1946), an observation which suggests the existence of distinct stages, still to be defined, in its action.

Surveying the results of this initial classification of antibacterial action, one can observe characteristic differences in the effects of different compounds but little specificity to agents successful chemotherapeutically, and no adequate understanding of the origin of the actions. The effects have in

many cases been ascribed to changes in hypothetical systems, and a physiological classification of such systems can be given in terms of their necessity for initiating or prolonging bacterial growth, or in terms of their necessity (in systems affected by bactericidal agents) or at least partial dispensability (with bacteriostatic agents) for maintenance of bacteria. Further advance has been based on such initial analyses, but has employed different techniques. The necessity for correct initial recognition of the physiological characteristics of antibacterial action may be illustrated by the lack of advance in understanding of the action of sulphonamides, while they were believed to be primarily bactericidal, or in that of penicillin, while it was believed to be primarily bacteriostatic.

BIOCHEMICAL AND CHEMICAL STUDIES

The main problem presented by the material of the foregoing paragraphs is the identification of the systems primarily affected by antibacterial agents. To approach this one may enquire to what extent growth is normally affected by chemical substances, apart from those artificially introduced. It is immediately found that many of the preceding effects can be paralleled by the action of substances normally associated with bacteria. Lag is increased by lowered concentrations of CO_2 (Gladstone, Fildes & Richardson, 1935; Dagley & Hinshelwood, 1938) or Mg^{++} (Lodge & Hinshelwood, 1939). Suboptimal concentrations of many substances essential to growth, including pantothenic acid (McIlwain, 1944), limit growth by a relatively specific action on the stationary population. Others affect growth-rate. It might therefore be possible to describe the systems attacked by inhibitors, in terms of the substances with which they normally interact.

Any investigation of the action of antibacterial agents meets at this point the complexity of living organisms, and the fact that more is unknown than is known of the nature and organization of their component systems. Empirical examination of the action of drugs on, for example, enzymes concerned with known nutrients would be extremely laborious and uncertain of yielding a positive result. Also, several inhibitory effects which have been discovered in this way have proved to be unconnected with the actions of the inhibitors on growth. Approaches which are more analytical and selective, and in some way specific to the particular agent concerned, are therefore required. Those which have been found successful do not conform to a single pattern, but are illustrated here by investigations of sulphonamide and acridine derivatives.

Sulphonamides and Drug-antagonists

Such an approach was found in the case of the *p*-amino-benzene sulphonamides, in the study of substances antagonizing their action. The inhibitory action of the drugs was found to be prevented by miscellaneous preparations of naturally-occurring materials, such as tissue or yeast extracts (Stamp, 1939), which did not, however, react with sulphanilamide in the absence of the bacteria. Supposing sulphanilamide action to have some degree of specificity, particular substances in the extracts might be expected to be associated with it. This proved to be the case and the main antagonist was shown to have the properties of *p*-aminobenzoic acid (Fildes, 1940; Woods, 1940). Here the selection of one compound related to the drug, from the many associated with living organisms, was achieved by chemical fractionation.

Degree of Action and Drug Concentration

The connexions frequently studied between such characters became of considerable value in the analysis of the action of sulphonamides, after *p*-aminobenzoic acid had been characterized. The discovery of this substance as antagonist was coupled with the finding of a rough proportionality between the concentrations of sulphanilamide and *p*-aminobenzoic acid needed to produce a given antibacterial effect, and the suggestion that this was due to competition between the two substances for essential bacterial systems. Such competition was expressed mathematically, assuming both compounds to be in equilibrium with such a system, and the rate of growth of *Escherichia coli* during its logarithmic phase was shown to be dependent on the quantity of *p*-aminobenzoate attached to the system (Wyss, 1941).

Assimilation and Function of *p*-Aminobenzoate

Some knowledge of this system has been obtained by considering the properties of *p*-aminobenzoic acid as it exists in bacteria. Organisms susceptible to sulphonamides may or may not synthesize *p*-aminobenzoic acid, but it exists in their cells in a combined form. If streptococci are grown in the presence of partly-inhibitory concentrations of sulphanilamide, they can suffer defects in major metabolic processes such as oxygen uptake (cf. Henry, 1943), but sulphanilamide cannot induce such deficiencies in already-grown cells. It does not displace from them a significant part of the *p*-aminobenzoic acid which they contain (McIlwain, 1945), but it does limit the cells in building up fresh cells containing *p*-aminobenzoic acid.

If sulphanilamide acts by inhibiting assimilation of *p*-aminobenzoic acid, the further question is raised of the manner in which this substance is essential to growth. Some suggestions regarding this have been made by a closer analysis of the course of growth of organisms in the presence of sulphonamides and of natural materials which antagonize their action. If complete growth-curves are followed, evidence for the occurrence of a type of antagonism different from that of *p*-aminobenzoic acid is found (Kohn & Harris, 1941, 1943, Harris & Kohn, 1941). This also can be ascribed to particular substances of natural occurrence, among which are methionine, certain purines, and further substances still unidentified. It is suggested that these compounds are the normal products of systems in which *p*-aminobenzoic acid functions, but the necessary biochemical demonstration of this is lacking.

For an approach to a full understanding of the action of sulphanilamide it will be necessary also to connect such findings with physiological features in the action of the inhibitors. Are methionine and purines less necessary during reactions of the lag-phase in bacterial growth, on which sulphanilamide has less action, than during the logarithmic phase, which is more susceptible to inhibition? The observation that methionine and purines are components of major cell-materials, such as proteins and nucleic acids, may be a partial answer, but detailed connexions between such observations and the defective respiration referred to above remain to be discovered.

Structural Specificity of the Inhibiting Agent

Sulphonamides have been discussed above collectively, but quantitative differences between the activities of differently-substituted *p*-aminobenzene sulphonamides have

given evidence confirming that their main action is related to *p*-aminobenzoic acid. Investigation of the action of drugs, by examining a series of related compounds so that connexions can be found between their structure and action, is a well-established method, and one which follows naturally from that empiricism in chemotherapy which has demanded the production of many compounds before effective ones have been found. Connexions between structure and action in themselves give only limited information, but if a relationship is suspected between an antibacterial action and further characteristics in the action of a drug, then the degree to which the two features are correlated in a series of chemically-related compounds gives evidence on the validity of the suspected relationship.

The first characteristic in the sulphonamides to be connected with the differing abilities of the drugs to inhibit bacteria was the interacting ratios of the concentrations of the drugs and *p*-aminobenzoic acid (see above, Rose & Fox, 1942). This confirmed the importance of *p*-aminobenzoic acid in their action. The second characteristic so correlated was the acidic-dissociation constant of the drugs. This property was selected for investigation on the basis of the finding that action of sulphonamides was related to *p*-aminobenzoic acid through competition for a common system of the bacteria, it was considered that competition would be effective in so far as the sulphonamide approached *p*-aminobenzoate in its behaviour as an ionized amino-acid. Here a marked optimum in antibacterial activity at pH 7 was found to be associated with a *pK*_a of 6.5 (Bell & Roblin, 1942). This finding was of considerable value, as through the known effects of substituents on the ionization of aromatic derivatives, it enabled the probable action of unknown substances to be predicted.

Structural Specificity in the Action of Acridine Derivatives

This latter phase in the investigation of the action of sulphonamides has been paralleled in that of acridine derivatives. In this case, knowledge of the physical property likely to be concerned in their action was not obtained on the basis of prior biochemical investigation, but by studying several such properties in over 100 acridine derivatives (Albert, Rubbo, Goldacre, Davey & Stone, 1945). Several organisms of varying susceptibilities to the inhibitors were examined, but the relative activities of the compounds were roughly the same in each organism, it was concluded that their actions in the different organisms were also similar. Among the different compounds, structures capable of resonance were frequently associated with high antibacterial activity, but not always, lipophilic nature was not markedly correlated with antibacterial properties, and redox potential appeared of secondary and not primary importance. The closest correlation with antibacterial properties was found in the basic strengths of the compounds. The effect of substituents in the acridine molecule, upon antibacterial action in the resulting compounds, could largely be determined by their effect upon basic strength. Amino-groups in the 2- and 5-positions increased both properties, in chloro-derivatives, both were depressed unless the compounds substituted were already highly ionized, hydroxyl-groups also depressed both properties. Nitro-groups were exceptional in introducing discrepancies into the above correlation, presumably through action of a different type from that typical of the acridine nucleus.

These findings were summarized in the conclusion that only those compounds of basicity sufficient for some 75% of the acridine to be present as cations at pH 7.3 were effective antibacterial agents. As the effects of substituents on the basic strength of aromatic molecules is known from independent data, in at least a semi-quantitative fashion, it was possible for the probable antibacterial potency of unknown molecules to be indicated and to afford a guide in synthesis.

Antibacterial action in the acridines fell with decrease of pH in a manner which was quantitatively interpreted as a competition between H⁺ ions and the bases, for essential sites on the bacteria. Growth or absence of growth was conditioned by the balance of the reactions (R being a bacterial grouping and A an acridine derivative) $R^- + H^+ \rightleftharpoons RH$ (capable of functioning) and $R^- + A^+ \rightleftharpoons RA$ (inactive). Little can be said of these groupings, from the present results, except that they are presumably acids with properties in some way related to the acridine nucleus, for not all bases act as do the acridines.

Antagonists to the Action of Acridine Derivatives

At this point some independent characterization of the bacterial system affected by acridine derivatives was required. Study of antagonists to the action of the compounds has not been as productive as was the case with sulphonamides, but has given some relevant data. Firstly, the naturally-occurring substances most potent in antagonizing proflavine (2,8-diaminoacridine) are nucleic acids, which act by forming with it complex salts (McIlwain, 1941). These are not necessarily precipitated, but reduce the concentration of proflavine ions in solution, superimposing on the equilibria of the preceding paragraph the further one ($N^- =$ nucleic acid ion) $N^- + A^+ \rightleftharpoons NA$, through which some of the acridine derivative is withdrawn from the bacteria. Organisms exposed to proflavine until they were non-viable under ordinary conditions could be rendered viable by exposure to nucleic acids. Both the quantities of nucleic acid needed as antagonist, and features in the action of the acridines, suggest that their action is not to combine with all nucleic acids of the organisms, but with, for example, certain specific nucleic acids.

As with the sulphonamides, different types of compound have been found to antagonize only limited concentrations of proflavine. In the case of *Escherichia coli*, one of these antagonists had the properties of an amino-acid but was not chemically identified (McIlwain, 1941). With *Bact. lactis aerogenes* such an antagonist was found to be of importance in the normal growth of the organism (Davies, Hinshelwood & Pryce, 1944). The main effect of proflavine on the bacterium was to increase the length of its lag-period. This could also occur independently of antibacterial agents, it was found in the growth of an inoculum taken from a very young culture, and was then annulled by addition of a sterile filtrate from an older culture. Such a filtrate would also prevent the increased lag due to proflavine. Substances of the filtrate were presumably normal products of bacterial enzymes, which may thus be concluded to be inhibited by proflavine. Here, also, the possibility is afforded of biochemical characterization of the system concerned. The filtrate did not antagonize all actions of proflavine, the cells remained morphologically distorted.

OBSERVATIONS ON THE INVESTIGATION OF ANTIBACTERIAL ACTION

From these and other examples, some general observations may be made with respect to current studies of antibacterial agents. It is apparent that the effect of any one agent is to be traced through many consecutive systems of the bacteria, and, indeed, study of such agents is making considerable contributions to understanding the organization of living systems in general.

Considering such systems and commencing with the initial point of action of the agent, it will be seen that the "receptors" of earlier investigators are now usually regarded as enzyme-systems. Probably not sufficient investigations have been carried out to show any limitations to this view, but it has been of great practical and theoretical value. In particular, it has enabled the gap between added substance and bacterial processes to be bridged by entities whose general properties are well known, although the isolation of a receptor concerned with antibacterial chemotherapeutic agents has not yet been achieved. Regarding drug-receptors as enzyme-systems has not only given a general understanding of the relationship between drug and bacterium, but has greatly assisted the quantitative study of their interaction. Structural relationship between certain antibacterial agents and compounds normally of importance to the organisms is not necessarily specific to this outlook, but investigation of such relationships has developed largely under the stimulus of enzyme theories.

¶ Connexion between the products of the enzymes considered to be initially affected, and the physiological behaviour of the bacteria, is not by any means immediate. With sulphanilamide or pantooyltaurine the first action of the inhibitor appears to be on a system building up a further enzyme. The products of such an enzyme may be the substances of structural importance implicated as secondary antagonists to sulphonamides, or connected with energy-yielding reactions as in the case of pantooyltaurine, but it is apparent that many systems are involved whose isolation or further characterization is necessary before the actions can be said to be understood with any completeness.

In other instances—which include penicillin—investigations still require an initial directive comparable to that given to the study of sulphanilamide by the implication of *p*-amino-benzoic acid in its action. This stage would probably have been passed if the methods successful with sulphanilamide were directly applicable to penicillin. That element in the investigation of sulphonamides, pantooyltaurine, the anti-pneumococcal polysaccharidases and other agents, which is most probably of general application, is the great experimental value of establishing a connexion between their action and specific cell-constituents. Substance and process, here as elsewhere in living organisms, are interconnected aspects of the same entity, but, when neither is known, it is the substances that we can probably first characterize with greater certainty and precision. The development recounted above of knowledge of sulphonamide action illustrates how studies concentrating at one time on substances, and at another on processes, alternate and support each other. Study of antibacterial action is so far from being a stereotyped subject that the manner in which substances associated with new chemotherapeutic agents are characterized must depend on peculiarities of the agent concerned and on the genius of the individual investigator.

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THE NUTRITION OF BACTERIA

The Work of the Medical Research Council's Unit for Bacterial Chemistry

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Accurate knowledge of the nutrition of bacteria is of very recent date. At the time of the publication of the Medical Research Council's *System of bacteriology* (1929-31), it was understood that some bacteria of medical interest would grow on simple mixtures of salts in which the sole nitrogen source was NH_3 , and lactate or glucose supplied the energy. On the other hand, it was known that other bacteria required amino-N. If these nutrients were inadequate, then "peptone" in its various forms was used and, in the last resort, serum, blood and other products of the "medium kitchen". Those who were interested in the physiological aspects of nutrition—and they were few—had shown that an inadequate medium could be made adequate by the addition of extracts of organic material, and had even fractionated these extracts until the activity was so highly concentrated as to be capable of showing a biological effect in quantities as small as did an "accessory growth factor". It was certainly supposed that the minute "accessory" addition was a single substance, and the influenza bacillus which was known to require two accessory factors was looked upon as more complex. Much discussion had taken place as to whether these were bacterial "vitamins", comparable with the vitamins of animals.

Much the same position was taken up in the Medical Research Council's *Vitamins: a survey of present knowledge* (1932). The idea that bacteria required what may be called a balanced diet had not crystallized. Much work had been done on testing the reaction of bacteria to single substances as sole sources of carbon or nitrogen, but whatever interest such work may have it had clearly no practical nutritional significance.

Ten years later the position had been greatly clarified as a result of work largely confined to America and Britain, in the latter by the Medical Research Council through its *Unit for Bacterial Chemistry*.

It became widely recognized that bacteria require for normal growth, not only the same basic sources of energy as do animals, but the same sources of amino-nitrogen and, within limits, the same vitamins. The only outstanding difference between animals and bacteria is due to the fact that the latter have more power of adaptation to changed environments, and can thus develop more easily a power to synthesize materials which are normally essential, and so dispense with these in the nutrients.

Preliminary Work on Bacterial Metabolism

The Unit (Department) for Bacterial Chemistry was founded by the Medical Research Council in 1934 in the following circumstances. The present writer, in the part-time service of the Council and working at the London Hospital, had been interested for years in the more physiological aspects of bacteriology, e.g. in the conditions of growth of the influenza bacillus (Fildes, 1920, 1921, 1922, 1923, 1924), and then in the conditions allowing the germination of tetanus spores (Fildes, 1927, 1929a, 1929b, Campbell & Fildes, 1931). Being without special chemical training, he became associated with B. C. J. G. Knight to study the germination of spores with more accuracy (Knight & Fildes, 1930). It then became clear that advance in this direction was unlikely without more knowledge of the basic nutrition of bacteria. At that time conditions were not unpropitious. Biochemistry was making increasing contributions to bacteriology. Dr Marjory Stephenson, of Cambridge had produced the first edition of her book, *Bacterial metabolism* (1930), in which knowledge of bacterial nutrition was critically analyzed from the biochemical point of view. In the first two volumes (1932, 1933) of *Annual Review of Biochemistry* she published articles on the chemistry of bacteria, in which nutritional advance was however so small as to be unworthy of mention. In the same volumes Heidelberger wrote on immuno-chemistry. It was only in the third volume (1934) that the nutrition of bacteria was referred to. Here it is recorded that Mueller Klise, Porter & Graybiel (1933) in the USA had discovered that cystine and tryptophan were essential for the growth of *C. diphtheriae*, that Burrows (1933), also in the USA had

been growing *Cl botulinum* on mixtures of amino-acids, and that Fildes & Knight (1933) in Britain had made several advances

J. H. Mueller had been working on critical chemical lines for some years and, in fact, during his bacteriological studies, was the first to isolate a hitherto unknown substance, the amino-acid methionine, which later was shown to be an essential amino-acid for some microbes and, of course, for animals

When starting work, Knight and Fildes decided to avoid non-pathogenic bacteria which, being able to grow on ammonium lactate, were clearly unsuitable test-objects for the study of "accessory factors". They concerned themselves with the more exacting, usually pathogenic, types which, in any case, were the microbes in which the Medical Research Council was directly interested. *Cl tetani*, the germination of which had been under investigation, was, however, too "difficult", and work was transferred to *Cl sporogenes*, which had similar anaerobic characters

In due course they described a "Sporogenes vitamin" (Knight & Fildes, 1933), without which the organism would not grow. The chemical nature of this vitamin has never been established, in spite of the collaboration of Pappenheimer (1935), when he was on a visit to Britain and working at the Council's National Institute for Medical Research. In this respect the work of Knight and Fildes cannot be considered a major advance, but in the course of it they established to a large extent the amino-acid requirements of the organism. At that time, the impurity of natural amino-acids was a grave difficulty, and it was fortunate that W. C. Rose and his collaborators on animal nutrition laboured under the same disability in America, since this induced his colleague Marvel to evolve practical methods for the bulk synthesis of amino-acids. Gradually synthetic products are replacing the natural, but even to this day the series is not complete. The great importance of synthetic products for this type of work is shown by the fact that the growth of *Cl sporogenes*, obtained in 1933 by Knight and Fildes, cannot be repeated at the present time. It is clear that some other essential factor, present as a contamination in the natural products then used, has been eliminated from our present reagents

At this time Dr G. P. Gladstone joined the writer and Knight as a bacteriologist, and papers (Fildes, Gladstone & Knight, 1933, Fildes & Knight, 1933) were published showing the amino-acid requirements of *Bact typhosum* and recording the fact that the requirements changed on adaptation to a changed environment. The relation of tryptophan to nutrition was particularly stressed

Thus an organism which normally required tryptophan could be trained to require it no longer, by gradually removing tryptophan from the nutrient mixture. This derived organism was found to have acquired the power to synthesize the missing tryptophan from simpler compounds. It was also pointed out that "the parasitic or pathogenic habit is apt to be related to inability to synthesize tryptophane"

Formation of the Medical Research Council's Unit

These papers indicated the possibility of a new approach to some aspects of medical bacteriology, and the Medical Research Council decided to form a special unit for continued research under the direction of the present writer, including Dr Knight and Dr Gladstone, and strengthening

the biochemical side by the appointment of Dr G. M. Richardson

The Council was encouraged to take this step owing to the munificence of the Trustees of the late Viscount Leverhulme, who have maintained their support to the present day. The Council was also fortunate to receive a generous offer of accommodation for the Unit at the Bland Sutton Institute of the Middlesex Hospital, directed by Professor James McIntosh, an early colleague of the writer. This Unit was designed to be a partnership of bacteriologists and biochemists, working in adjacent rooms and in constant daily discussion. All papers published necessarily contained matter derived from or actually the work of anonymous colleagues

Work was started at the Middlesex Hospital in 1934. The Unit was largely responsible for establishing for the first time the essential amino-acid requirements of a number of bacteria and for showing that nutritional requirements depended upon a failure of synthesis. Out of this work the concept was gradually developed of an evolution of bacteria depending on a loss of synthetic function, a concept precisely similar to that advanced simultaneously but independently by Lwoff at the Pasteur Institute, Paris, in relation to protozoa

Whether the more speculative hypotheses on the evolutionary relations of animals and bacteria discussed by Fildes (1934) are rejected or not is of little importance, since they cannot be tested, but the data on which these were based—collected and correlated by Knight and published by the Medical Research Council (Knight, 1936)—created world wide interest and, in fact, have been an important influence in stimulating the chemical study of bacterial nutrition

The Unit became particularly involved in the nutrition of *Staph aureus*. Richardson (1936) found that uracil was a necessary nutrient in the anaerobic growth of this organism. This was probably the first instance in which a bacterial vitamin, other than an amino-acid, had been precisely defined. Knight (1935) had been working on another new "factor" necessary for growth, and was later (1937) able to show that his factor consisted of aneurin and nicotinamide. Schopfer (1935) had already shown that aneurin was an essential nutrient for a mould, and Tatum, Wood & Peterson (1936) that it was probably essential for lactic bacilli. Nicotinamide was, however, a new introduction into bacteriology. These results made it clear that the use of the expression "vitamin" in relation to bacteria, rather than the more favoured "hormone", was correct, since one of these substances was already accepted as an animal vitamin while the other was accepted very soon after

In the meantime Fildes & Richardson (1937) defined the sulphur requirements of staphylococcus, and Gladstone (1937) the nitrogen requirements and the conditions under which the haemolysin is produced (Gladstone, 1938). It was now possible for the first time to grow an exacting pathogen on a mixture of known composition

At this stage Dr G. M. Hills joined the Unit and established the necessity for aneurin in the pyruvate metabolism of *Staph aureus* (Hills, 1938). Dr Richardson left and was replaced by Dr H. McIlwain, who became associated in the discovery of glutamine (McIlwain, Fildes, Gladstone & Knight, 1939) and of pantothenic acid (McIlwain, 1939) as factors in the growth of *Strept haemolyticus*. In 1940 he was the first to grow *Strept haemolyticus* on a defined mixture (McIlwain, 1940a)

In the meantime, a study of the nutrition of *B anthracis*

revealed curious interrelationships between the nutrient amino-acids (Gladstone, 1939)

The Unit had repeatedly pointed out the close similarity between the amino acid and vitamin requirements of animals and bacteria, and suggested that at least the preliminary stages of animal nutritional research could be established with bacteria with a great saving of time—in hours rather than in weeks or months. According to Williams (1943), this practice is now common. Microbiological tests "have the tremendous advantage that the number of tests can be very large without an inordinate expenditure of time"

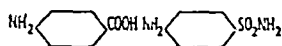
Influence of Bacterial Nutrition on Antiseptic and Chemotherapeutic Substances

Dr Knight had now left the Unit and had been replaced by Dr D D Woods, a member of the team directed by Dr Marjory Stephenson working on bacterial metabolism for the Council at the Biochemical Laboratory, Cambridge. At that time Dr L E H (now Sir Lionel) Whitby, a member of the staff of the Bland Sutton Institute, was collaborating with Dr A J Ewins on the testing of sulphonamide drugs, and informal discussions with the Unit were frequent. It seemed clear to the Unit that the action of an antibacterial drug might be by interference with the normal action of an "essential metabolite". The term "growth factor" had been abandoned in favour of this term, because the former was associated with nutrition, i.e. it was a substance which must be provided for a microbe which could not synthesize it. On the other hand, the same substance was an essential link in the metabolism of a microbe which could synthesize it, although it was not then required as a nutrient "growth factor".

The Unit had already shown that the group -SH was an essential metabolite, and since Hg is known to combine with -SH, it was not difficult to surmise that the antiseptic action of Hg might be due to this combination. It was also well known that the essential metabolite -SH (H-SH) could counteract or antagonize the antiseptic action of Hg. This hypothesis of the action of Hg was tested and found correct by Fildes (1940a).

In the case of sulphanilamide there was already evidence of the existence of "antagonizers" in extracts from bacteria (Stamp, 1939). These, in the view of the Unit, might well be essential metabolites on which sulphonamide reacted, but which in excess could antagonize sulphonamide.

This matter was taken up by Woods with the result that *p*-aminobenzoic acid was found to antagonize sulphonamide (Woods, 1940). According to Woods, *p*-aminobenzoic acid was an essential metabolite for bacteria, and the action of sulphonamide was due to interference with the normal metabolism of *p*-aminobenzoic acid, which, in turn, was due to the close structural similarity between these two substances —



It was a question of competition between sulphanilamide and *p*-aminobenzoic acid for the service of an enzyme concerned normally with the metabolism of the latter.

A Rational Basis for the Development of Chemotherapeutic Agents

This was clearly a discovery of major importance, with many repercussions outlined by Fildes (1940b). Among

other things, it indicated that competitive inhibitors might be designed to block the metabolism of any essential metabolite. It was only necessary so to modify the structure of an essential metabolite that it could no longer function as such, but still occupy the service of the enzyme. Thus, McIlwain (1940b) produced pyridine-3-sulphonic acid on the model of nicotinic acid and sulphonamide, and Fildes (1941) showed that indoleacrylate prevented growth by inhibiting the further utilization of indole, which substance he had found to be a stage in the synthesis of tryptophan (Fildes, 1940c). A rational procedure in the development of chemotherapeutic agents had thus been indicated, and at the same time a method for analyzing the stages of biosynthesis.

It was not given to the Unit to support the hypothesis by demonstrating the correctness of the prediction that *p*-aminobenzoic acid was a hitherto-unknown essential metabolite and animal vitamin, because it ceased work in the middle of 1940. Rubbo & Gillespie (1940) in Australia proved the first prediction and Ansbacher (1941) the second. Of the Unit, only Dr McIlwain, at the University of Sheffield, continued this work.

Continuation of the Work in the United States during the War

During the war years the members of the Unit have watched the development of this subject in America with interest. The discovery of new bacterial vitamins has become almost a matter of routine, and the application of these discoveries to animal nutrition has become general. Van Niel (1943) states "It is almost a foregone conclusion that a newly discovered growth factor, needed in minute amounts by some micro-organisms, will soon be shown to be a vitamin for higher organisms".

It would seem that the general hypothesis of the Unit, relating antibiotic action to the structure of essential metabolites, has been supported by many new instances and generally accepted. Thus, Daniels (1943) "From the standpoint of biochemistry, the most interesting development in this class of compounds is the elucidation of a mechanism that allows one to correlate the activities of these compounds with their physico-chemical properties. Earlier postulates relating to the mechanism of action have been more or less superseded by the theory of Woods and Fildes".

Van Niel (1943) "It must be recognized that the attempts to produce new bacteriostatic agents as analogues of known growth factors have resulted in products whose activity is, on the whole, so well in agreement with expectation that the fruitfulness of the original concept has been established."

Williams (1943) "While it must be admitted that the new approach to chemotherapy has not, as yet, led to the discovery of new therapeutic agents of outstanding merit, it seems likely that a more thorough study of the fundamental facts concerned will bear fruit."

In view of these opinions, too much attention need not be paid to the few objectors. There has been a tendency to generalize far beyond any claims made by Woods in his only contribution to this subject (1940).

The Unit had just embarked upon the analysis of the stages in the biosynthesis of essential metabolites, using bacteria which were, spontaneously or by training, devoid of certain synthetic enzymes. This subject has now made great progress in America through a new technique of employing the mould *Neurospora*, in which single synthetic enzymes have been destroyed by the action of x rays. The

importance of this work rests on the fact that any stage in the synthesis of an essential metabolite is itself an essential metabolite and, further, one against which a competitive inhibitor can be designed

Present State of Knowledge of Bacterial Nutrition

At the present time the general background of bacterial nutrition has been established, although there are lacunae to be filled. One can say that nutrients are required in the last resort to allow bacteria to reproduce and, of course, to carry on functions of which the appointed end is reproduction. These activities require free energy and the basic materials from which new protoplasm, of the type specific to the bacterium, can be built.

If the argument is confined to the more or less heterophilic bacteria which include those of medical interest, we can say that the science of nutrition defines the precise chemical ingredients which must be absorbed by a bacterium so that (a) it can liberate free energy from them by katabolic enzymes and (b) build up protein from them by synthetic enzymes.

In order that the bacterium may absorb these ingredients they must be of a molecular size small enough to allow diffusion into it.

The mechanisms by which energy is liberated have been studied for years under the heading of "bacterial metabolism", and the Unit has had little concern with this aspect of the subject. Its chief interest has been in the synthetic processes.

Here we have nitrogen-containing substances of small molecular weight, even as small as ammonium salts, and inorganic substances containing the other essential elements. These are absorbed by bacteria and in a few hours synthesized to protein. This remarkable feat is, of course, not achieved in one step, but in a series of steps, each achieved by a separate synthetic enzyme.

Some bacteria have a full battery of these enzymes, so that they can proceed from NH_3 to protein unassisted. Other bacteria have not, and in this case cannot grow because the synthesis is blocked at the level of the enzyme deficiency.

It is these bacteria that throw light on nutrition, because they can grow only when the missing component is supplied to them preformed as a nutrient. This is the "growth factor" singled out by a particular bacterium, from all the other "essential metabolites" in the synthetic chain, by the fact that it cannot synthesize it.

Plans for Resumption of the Unit's Work

The Medical Research Council is now concerned with reconstructing the Unit to continue this work and develop it along such lines as may be possible. Necessarily, there must be a long period of delay before results can flow. With the lapse of time, normal dispersal of personnel has taken place, Dr G. P. Gladstone being the only survivor of the original Unit to assist in reconstruction. Dr Woods is now organizing a new group at the University of Oxford, Dr McIlwain remains at the University of Sheffield, and Dr Hills is stationed at the Microbiological Research Department, Porton. Their places have been taken by Dr H. N. Rydon, Dr M. R. Pollock and Dr D. Herbert. The former premises at the Middlesex Hospital, although little affected by the War, are now too small, and arrangements have been made to house the Unit at the Lister Institute of Preventive Medicine, where work will gradually develop as the present austere conditions improve.

The object of the Council in reconstructing the Unit may be supposed to be the discovery of fundamental knowledge of the physiological reactions of bacteria. Normally, work of this sort would be the concern of universities rather than of a Government Department charged with research for the alleviation of the sick, but in Britain bacteriology has always been so bound up with medicine that the universities have made little provision for it. The Council has long recognized that the application of research to the needs of man requires capital, and that this capital is the knowledge collected by those who work without any obligation to achieve utilitarian ends. They have thus taken over the duty of universities, or have at least by their example and assistance to universities started a movement which will provide material suitable for exploitation.

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MICROBIAL RESISTANCE TO CHEMOTHERAPEUTIC DRUGS

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Micro-organisms vary widely in their natural susceptibility to chemotherapeutic drugs, and this is particularly true of different species of bacteria, as is well shown by the relative insensitivity of the gram-negative bacilli to many of these agents. Natural variations in sensitivity are also common within the same species, thus, of 157 strains of *Staphylococcus aureus* isolated from clinical infections 9% were at least 8 times more resistant to penicillin than the average staphylococcal strain (Selbie, Simon & McIntosh, 1945). Such differences in natural susceptibility, not only to penicillin but also to the sulphonamides and other drugs, are encountered in many types of pathogenic micro-organisms and present a problem of considerable importance in chemotherapy. Naturally-occurring drug-resistant strains of micro-organisms, however, are usually unsuitable for investigation because their past history is usually unknown, and our knowledge of drug-resistance has therefore been derived mainly from the study of micro-organisms that have become resistant during the course of test-tube experiments or during the treatment of experimental or clinical infections.

The experimental method used in developing resistance to drugs and other toxic substances has in general consisted in exposing the micro-organism to increasing concentrations of

the substance in serial subcultures, or by passage in animals which are treated in successive passages with increasing doses of a chemotherapeutic agent. The first experiments of this kind were done by Ehrlich and his colleagues in their studies on the development of resistance to dyes and arsenical drugs in trypanosomes, and in recent years this method has been extensively used in the study of bacterial resistance to the sulphonamides and penicillin. This method, however, has also been used with many other toxic substances, and Table I shows some of the many drug-resistant micro-organisms that have been developed in this way. Yeast has also been made resistant to pyriminamine (Woolley & White, 1943), and tissue-cultures of metazoan cells have acquired increased tolerance to copper sulphate and sodium arsenite (Wilson, 1922) and to sulphonamides (Jacoby, Medawar & Willmer, 1941).

It would thus appear that the ability to acquire tolerance to toxic substances is a common biological property of living cells and that the mechanism underlying the development of resistance is probably unspecific, particularly in view of the multiplicity of agents to which resistance can be acquired.

Drug-resistance in Trypanosomes

The development of drug-resistance was first observed in mice infected with *Trypanosoma brucei* by Browning, Franke and Roehl (Ehrlich, 1907; Browning, 1907), who found that the trypanosomes which appeared in the blood in relapses after treatment with paraformal required more and more of the dye to ensure disappearance after successive relapses, until safe doses of the dye were no longer effective. It was soon found that in trypanosomes resistance could be developed to other toxic substances, and that resistance could be increased by transferring the resistant relapse strains to other mice which were then treated with increased doses of the appropriate drug. Trypanosomes made resistant to drugs in this way were later shown by *in vitro* tests to survive higher concentrations of the appropriate drugs than the parent sensitive strains (Mesnil & Brimont, 1908; Ehrlich, 1909a; Neven, 1909) and could thus be differentiated from trypanosomes that were resistant to treatment by having become tolerant to specific antibodies, a type of acquired resistance that was demonstrated in trypanosomes by Ehrlich (1909b) and Levaditi & McIntosh (1910).

Drug-resistance in trypanosomes can also be demonstrated by their reduced affinity to dyes and other compounds. Trypanosomes resistant to a particular dye remain colourless when placed in solutions of the dye and allied compounds, whereas the normal parent strain of trypanosomes becomes deeply stained. Similarly arsenic-resistant trypanosomes have been shown by Levaditi (1909) in collaboration with McIntosh and by Yorke, Murgatroyd & Hawking (1931) to fix less arsenic than normal trypanosomes. Resistance to aromatic arsenical drugs in trypanosomes is also accompanied by resistance and diminished affinity to acridine, oxazine and other dyes (Ehrlich, 1909b; Gonder, 1912a), so that it would appear that resistance is directed not against arsenic but against the side-chains in the phenyl radical. Drug-resistance in trypanosomes would therefore seem to be due to a failure in the primary fixation of the drug, and not to interference with the final toxic action of the drug on some essential substrate.

Another change that has been noted in trypanosomes during the development of resistance to acridine and oxazine dyes is a disappearance of the parabasal body or blepharo-

TABLE I. EXAMPLES OF MICROBIAL RESISTANCE TO DRUGS

Drug	Organism	Reference
Optoquine	Pneumococcus	Morgenroth & Kaufmann 1912 Lewy, 1925
Lysozyme	<i>M. lysodeikticus</i>	Fleming & Allison 1927
Acriflavine } Methyl violet }	Staphylococcus	Burke, Ulrich & Hendrie 1928
Proflavine } Propamidine } Quindoline }	Staphylococcus	McIntosh & Selbie 1943
Gramicidin	Staphylococcus	Philips & Barnes 1942
Tyrothricin	Staphylococcus	Rammelkamp 1942
Streptomycin	Gonococcus	Miller & Bohnhoff 1946
Streptomycin	Meningococcus	Miller & Bohnhoff 1946
Arsenic	<i>Sp. recurrentis</i>	Margulies 1910 1912b 1934 Fischl & Singer
Arsenic	<i>Sp. gallinarum</i>	Margulies 1910 1912b Gonder
Gold	<i>Sp. recurrentis</i>	Fischl & Singer 1934

plast (Werbitzki, 1910, Kudicke, 1911, Laveran & Roudsky, 1911). There has been considerable discussion on the meaning of this structural change, but it would certainly appear to signify that there has been a variation or mutation during the development of resistance. Evidence that resistance can arise from natural variation is also afforded by the sudden appearance of arsenic-resistance in trypanosomes during passage in normal animals (Morgenroth, 1924, Browning, 1931). A recent and well-documented report by Eagle & Magnuson (1944) on a strain of trypanosomes that spontaneously acquired arsenic-resistance is of particular interest, because this strain displayed the same characters of reduced affinity to drugs and chemical specificity as are shown by experimental arsenic-resistant strains. It would therefore appear probable that the mechanism underlying the development of drug-resistance in trypanosomes is that of a progressive selection of spontaneous variants, the drug allowing the survival of only the more resistant variants. Further discussion on this problem and on the question of the specificity of drug-resistance is to be found in the communications of Browning (1931), King & Strangeways (1942) and Eagle & Magnuson (1944).

Resistance to Sulphonamides

The development of resistance to sulphonamides was first reported by Maclean, Rogers & Fleming (1939), who found an increase of resistance in pneumococci from patients undergoing treatment with sulphapyridine. Since then there have been numerous reports of increased resistance to sulphonamides during the treatment of clinical infections and, but for the advent of penicillin, sulphonamide-resistance in gonorrhoea would have become a problem of grave epidemiological importance. Among the first studies on the development of resistance to sulphonamides by experimental methods were those of MacLeod & Daddi (1939) on pneumococci, Chandler & Janeway (1939) on streptococci and Green (1940) on *Br. abortus*. Sulphonamide-resistance has since then been developed experimentally in many other types of bacteria, including staphylococci, *Neisseriae*, *Corynebacteria*, *Haemophili*, organisms of the coli-typhoid group, and even in one of the larger viruses, that of lymphogranuloma venereum (Jones, Rake & Stearns, 1945). Sulphonamide-resistance is in general agreed to be irreversible, whether it is natural or acquired.

MacLeod (1939) has reported that the *in vitro* development of resistance in pneumococci is associated with a loss of the power to dehydrogenate glycerol, lactate and pyruvate and with the production of less hydrogen peroxide. Kohn & Harris (1942) have observed that sulphonamide-resistant bacteria are more exacting in their nutritional requirements, while Sevag & Green (1944) have associated sulphonamide-resistance with an alteration in glucose metabolism. On the other hand, Wyss, Strandkov & Schmelkes (1942) have shown that the *in vitro* development of sulphanilamide-resistance in *Bact. coli* did not reduce the susceptibility of respiration in the resting cells to inhibition by sulphanilamide.

Of greater interest, however, is the finding that in some bacteria the development of resistance is accompanied by increased production of substances that inhibit the antibacterial action of the sulphonamides. This was first observed by the American worker, MacLeod (1940), in pneumococci that had acquired resistance to sulphapyridine *in vitro*, and it was confirmed by Tillett, Cambier & Harris (1943) with MacLeod's cultures, but not with two sulpha-

mide-resistant strains of pneumococci from clinical cases. A similar finding was made in sulphanilamide-resistant *Br. abortus* by Green (1940), and Green & Bielschowsky (1942) were able to identify part of the sulphanilamide inhibitor produced by resistant *Br. abortus* with *p*-aminobenzoic acid, following Woods' (1940) demonstration of the anti-sulphonamide properties of this substance and his suggestion that sulphonamide-resistance in bacteria might be due to increased production of *p*-aminobenzoic acid.

Further evidence of this mechanism of resistance in staphylococci has been provided by Landy, Larkum, Oswald & Streightoff (1943) who, using a microbiological test for *p*-aminobenzoic acid with *Acetobacter suboxydans* (which requires this substance for normal growth), have found that staphylococci which have developed resistance to sulphanilamide produce more *p*-aminobenzoic acid than the parent sensitive cultures. This property of sulphonamide-resistant staphylococci has been confirmed by Spink, Wright, Vivino & Skeggs (1944), and by Housewright & Koser (1944), who find that the production of *p*-aminobenzoic acid increases *pari passu* with the development of sulphonamide-resistance.

Similar findings have been made in cultures of gonococci rendered resistant to sulphonamide by Stokinger & Charles (1942) who, however, are of the opinion that the increased production of *p*-aminobenzoic acid does not account for the sulphonamide-resistance because the addition of azochloramide, which inhibits *p*-aminobenzoic acid, fails to overcome the resistance of the gonococcal cultures to sulphonamides. Landy & Gerstung (1944) have also measured the synthesis of *p*-aminobenzoic acid by gonococci isolated from 17 patients subsequently treated with sulphathiazole, and have found that in general greater amounts are synthesized by strains from patients that are resistant to treatment.

Increased production of *p*-aminobenzoic acid is, however, a far from constant finding in sulphonamide-resistant bacteria. Among the findings negative in this respect are those of McIntosh & Selbie (1943) with streptococci, Tillett, Cambier & Harris (1943) with pneumococci, Landy, Larkum, Oswald & Streightoff (1943) with *Bact. coli*, *Vibrio cholerae*, *Sh. dysenteriae* and pneumococci, and Housewright & Koser (1944) with *Sh. paradysenteriae* and pneumococci. It would thus appear that it is only in some bacteria that sulphonamide resistance can be ascribed to an increased production of *p*-aminobenzoic acid, which counteracts the interference of sulphonamides with the metabolism of this substance (Woods, 1940). In other bacteria, it is possible that another type of sulphonamide-inhibitor is produced which cannot at present be detected, or that their metabolism is so altered that the use of *p*-aminobenzoic acid can be dispensed with.

A good example of different mechanisms being involved in the development of resistance has been given by McIlwain (1943). He finds that resistance to the toxic substance pantooyltaurine in *C. diphtheriae* depends on the ability of this organism to synthesize pantothenate, which is a specific inhibitor of pantooyltaurine in much the same way as *p*-aminobenzoic acid is an inhibitor of sulphanilamide. Whereas pantooyltaurine-resistant streptococci differ from their parent-sensitive strains in possessing metabolic processes which are alternative to those involving pantothenate and are susceptible to inhibition by salicylate. The mechanism of sulphonamide-resistance in some bacteria may also prove to be of a less specific nature, such as lessened permeability and thus be in a sense comparable to the mechanism of drug-resistance in trypanosomes, where resistance is directed

against the access of the drug rather than against its specific toxic action on the sensitive substrate

There have been conflicting reports on the effect of the development of sulphonamide-resistance on the virulence of bacteria to experimental animals. MacLeod & Daddi (1939) have found no change in virulence in pneumococci or streptococci rendered resistant to a sulphonamide by the *in vitro* method. Horsfall (1942), however, has observed a considerable reduction in virulence in pneumococci after the *in vitro* development of resistance to sulphathiazole. This has also been the experience of Schmidt, Sesler & Dettwiler (1942) in sulphonamide-resistance experiments with pneumococci, using the *in vitro* method, but the same strains of pneumococci have shown no appreciable loss of virulence after the induction of resistance by passage through treated mice. Spink, Hall & Ferris (1945) also find that staphylococci retain their virulence after having acquired resistance to sulphonamides by both the *in vitro* and *in vivo* methods. The available evidence thus indicates that the *in vitro* method of developing resistance may lead to a loss of virulence, whereas the *in vivo* method has apparently little or no effect.

Penicillin-resistance

Acquired resistance to penicillin was first observed by Abraham, Cham, Fletcher, Florey, Gardner, Heatley & Jennings (1941), who induced penicillin-resistance in staphylococci by the *in vitro* method. Other workers have induced penicillin-resistance by *in vitro* and *in vivo* methods in staphylococci, and also in pneumococci, streptococci, meningococci and gonococci. Increased bacterial resistance to penicillin has also been observed during the treatment of clinical cases with penicillin, especially in staphylococcal infections, but the increases in resistance that have so far been encountered do not appear to have interfered with the efficacy of treatment, provided that the dosage of penicillin is adequate (Selbie, Simon & McIntosh, 1945). Penicillin-resistance that has been developed by cultural methods has proved reversible in the hands of Todd, Turner & Drew (1945) with staphylococci and streptococci, but not pneumococci, and this finding has been confirmed in the case of staphylococci by Spink, Hall & Ferris (1945). Loss of resistance to penicillin, however, has not so far been observed in bacteria that are naturally resistant or have acquired resistance in patients or animals undergoing treatment with penicillin.

Some of the modifications that have been found in association with the development of resistance to penicillin are an increase in size of staphylococci (Smith & Hay, 1942) and a reduction in growth-rate and enzymic activity in staphylococci (Abraham *et al.*, 1941) and in pneumococci (McKee & Houck, 1943). Of greater importance, however, is the evidence that resistance may be related to the production of penicillinase, the penicillin-destroying enzyme first isolated from gram negative bacilli by Abraham & Chan (1940). Rake, McKee, Hamre & Houck (1944) were unable to detect the production of penicillinase by staphylococci that had been made resistant to penicillin, and this has also been the experience of Spink, Hall & Ferris (1945) and Bondi & Dietz (1946). In staphylococci isolated from clinical infections, however, Kirby (1944), Bondi & Dietz (1945) and Gots (1945) have shown that penicillin-resistant strains almost invariably produce considerable amounts of penicillinase. That resistance in many of these strains of staphylococci is due to the production of penicillinase has been demonstrated by

Luria (1946), who finds that, when tested *in vitro* with small inocula, they are fully sensitive to penicillin, their growth being inhibited before sufficient penicillinase is produced to destroy the penicillin. There are organisms, however, which are normally highly resistant to penicillin and are apparently unable to produce penicillinase, such as *Bact. typhosum* and certain organisms of the salmonella group (Bondi & Dietz, 1944). It would thus appear that, although the production of penicillinase may account for the natural resistance to penicillin of some organisms, it does not necessarily follow that the inability to produce penicillinase implies sensitivity, or that the development of resistance by experimental methods is associated with the increased production of penicillinase.

The effect of the development of resistance to penicillin on the virulence of bacteria seems to depend largely on the method used for inducing resistance, as has already been mentioned regarding sulphonamide-resistance. McKee & Houck (1943) have found that streptococci and pneumococci are greatly reduced in virulence to mice after being made resistant to penicillin by the cultural method and that virulence cannot be restored by passage through mice. In similar experiments with 7 strains of meningococci, Miller & Bohnhoff (1945) have also observed considerable and irreversible falls in virulence to mice during the *in vitro* development of resistance. On the other hand, there has been no decrease in virulence to mice in pneumococci or staphylococci that have been made resistant to penicillin by passage through treated mice (Schmidt & Sesler, 1943; Rake, McKee, Hamre & Houck, 1944).

This difference in the effect on virulence between the *in vitro* and *in vivo* methods of inducing resistance to penicillin and the sulphonamides is to be expected when consideration is taken of the environmental conditions. The virulence of bacteria tends to fall with repeated sub-culture, particularly when the medium is unfavourable as is the case here, where sub-effective concentrations of a bacteriostatic agent are used for the induction of resistance. On the other hand, the passage of bacteria through animals tends to maintain or increase virulence so that, in the *in vivo* method, resistance is developed only in organisms that are adapted to survival in the host tissues. The influence of this factor is well shown in the experiments of Rake, McKee, Hamre & Houck (1944), where a strain of staphylococci, rendered resistant to treatment by passage through penicillin-treated mice, was, however, fully sensitive to the action of penicillin *in vitro*, and must therefore have been resistant to treatment by having adapted itself to the antibacterial action of the tissues of the mouse. In this respect the situation regarding the *in vivo* development of resistance in bacteria to treatment with chemotherapeutic agents is similar to that afforded by the development of serum-resistance in trypanosomes which, as has already been mentioned, has long been recognized as a complicating factor in the assessment of drug-resistance (Browning, 1931).

Cross-resistance

It has been stated that, when an organism is resistant to one sulphonamide, it is correspondingly resistant to all other sulphonamides. It is now recognized that, although there may be some cross-resistance within the sulphonamide group, it is not quantitatively complete (Kirby & Rantz, 1943), and Colebrook (1943) has shown that, of 7 strains of streptococci resistant to sulphonamide, only one was resistant to three

other sulphonamides and six were fully sensitive to sulphathiazole. This lack of complete cross-resistance within the sulphonamides is to be expected if one assumes, as has been suggested here, that the mechanism of sulphonamide-resistance may vary from one organism to another.

It has been agreed by many workers that an organism that has acquired resistance to one drug, such as penicillin or one of the sulphonamides, still retains its sensitivity to other unrelated drugs. McIntosh & Selbie (1943), however, showed that staphylococci made resistant to proflavine (2,8-diaminoacridine), or to the unrelated drug propamidine, were resistant to both compounds, while proflavine-resistant cultures had acquired no increased resistance to the closely related compounds 2,7-diaminoacridine and 5-aminoacridine. The two latter compounds also differed from proflavine, in that resistance to them could not be developed in staphylococci. Albert, Rubbo, Goldacre, Davey & Stone (1945) have suggested that these differences may be only a measure of the facility of the resistant organisms to destroy a drug by oxidation or deamination, and that it would therefore be impossible to develop resistance to such a highly stable substance as 5-aminoacridine. In any case, it is apparent from the close relationship between resistance to proflavine and propamidine that resistance is directed against the side-chains in much the same way as has already been mentioned regarding the resistance to dyes of arsenic-resistant trypanosomes. McIntosh & Selbie also found that two cultures of staphylococci that were made resistant to quindoline methochloride differed, in that one was also highly resistant to propamidine whereas the second showed no such cross-resistance. This finding again shows that organisms may develop resistance to the same drug in different ways.

Mechanism of Development of Resistance

The process involved in the development of drug-resistance does not appear to be one of selection from resistant organisms already present in the parent culture, because the organisms in the final resistant culture are more resistant to the drug than any single member of the original culture (McIntosh & Selbie, 1943). This process must therefore involve an adaptation of the organism to the presence of the drug so that it becomes less sensitive. The adaptation of the organism, however, does not appear to be a specific response to the drug, because organisms made resistant to the same drug can differ in their mechanism of resistance and in other properties. Such differences are to be found in the production of *p*-aminobenzoic acid or penicillinase in sulphonamide- or penicillin-resistant bacteria, and in the effects of the development of resistance on virulence.

The mechanism underlying the development of resistance would therefore appear to be of an unspecific nature, and is probably an aspect of the capacity for spontaneous variation or mutation which is a property common to all micro-organisms. Evidence in support of this view has been adduced by Demerec (1945), who finds that the development of resistance to penicillin in staphylococci is proportional to the mutation-rate. Further supporting evidence is given by Carpenter, Bahn, Ackerman & Stokinger (1945) in their *in vitro* experiments on the induction of resistance in 7 strains of gonococci with single drugs and mixtures of drugs. When single drugs were used, the average increases of resistance that were obtained with sulphathiazole, rivanol lactate,

promin and penicillin were 700-, 80-, 9- and 182 fold respectively, but when resistance was induced in a mixture of the first three drugs, there was only an 8-fold increase in resistance to each of the three drugs, and when all four were used there was no increase of resistance to any of the four drugs. On the other hand, resistance to more than one drug can be elicited in an organism with ease, provided that the drugs are presented successively (McIntosh & Selbie, 1943).

These results are consistent with the view that the development of resistance depends ultimately on spontaneous variation, because the chance of the appearance of a successful variant would be progressively lessened as the number of factors required simultaneously for success was increased, the requisite factors here being resistance to different drugs. The role of the drug in the development of resistance would then be to eliminate the more sensitive organisms, and allow the survival of only the more resistant variants, and would thus be in a sense similar to the part played by lactose in providing a preferential medium for the encouragement of the growth of the spontaneous lactose-fermenting variants of *Bact. coli-mutabile* (Lewis, 1934). The process of the development of drug-resistance could thus be described as a progressive selection of spontaneous variants which have increased resistance to the drug.

Resistance in Clinical Infections

It is remarkable that, in spite of the widespread use of the sulphonamides and penicillin, there are relatively few instances in which organisms have been proved to have developed drug-resistance during the treatment of clinical infections. Furthermore, the development of resistance has been observed mainly in pneumococcal and staphylococcal infections, and rarely, if ever, in streptococcal infections. It would thus appear that some organisms are more prone than others to develop resistance in clinical infections, but it may be that the determining factor is the nature of the lesion. Thus, the relative avascularity of staphylococcal lesions would prevent the access of a bacteriostatic concentration of the drug to the infecting organism, and would thus provide the conditions necessary for the development of resistance (Hudson, Meanock, McIntosh & Selbie, 1946). In the case of streptomycin, however, the development of bacterial resistance occurs readily during the treatment of clinical infections (Buggs, Bronstein, Hirshfeld & Pilling, 1946), but this chemotherapeutic agent is exceptional, in that cultures of bacteria can acquire resistance to its action with extreme rapidity (Miller & Bohnhoff, 1946).

Increased resistance to treatment in clinical infections may be due to factors other than the development of resistance in the infecting organism. The original susceptible organism may be eliminated and replaced by a less susceptible type. This has been found by Siegel & Karr (1945) to occur during the prophylactic use of sulphadiazine in an epidemic of pneumococcal infections in children, and in the suppression of throat streptococci in naval training schools by Damrosch (1946).

The remarkable increase in the resistance of gonococcal infections to sulphonamide treatment may also be due to the gradual elimination of the more sensitive strains, so that only the more resistant strains are propagated. In support of this view is the American observation that the anticipated war-time rise in gonorrhoea has not occurred (Mahoney & Van Slyke, 1945), so that it must be presumed that the

sources of infection have been greatly reduced by sulphonamide therapy. It has also been observed by Harkness (1944) and Mahoney & Van Slyke (1945) that gonococcal infections may be highly resistant to sulphonamide treatment, although the infecting organism is fully sensitive to the drug *in vitro*, and it has been found that the serum of some of these cases

contains a substance that counteracts the action of sulphonamides *in vitro* (Harkness, 1943)

It is thus evident that in the assessment of the development of resistance to treatment in clinical infections there are other factors to be considered before it can be concluded that the infecting organism has acquired drug-resistance

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CHEMOTHERAPY OF RICKETTSIAL AND VIRUS DISEASES

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The essential nature of the smaller viruses is much disputed the larger ones are generally agreed to be closely related to bacteria. They behave as obligate intracellular parasites of animals, higher plants or bacteria, and have not yet been cultivated outside the living cells of their host. They seem to have virtually no active metabolism when outside their host cell what happens inside is hard to determine. Though smaller than most bacteria, viruses cannot be defined solely on a basis of size or filterability, for the largest are larger than the smallest bacteria. Between the main body of the viruses and the bacteria lie two fairly distinct groups, the rickettsiae and the viruses of the psittacosis group (Andrewes, 1944). The rickettsiae are conventionally excluded from the true viruses, they are arthropod-transmitted, often rod-shaped, and show, many of them, antigenic cross-reactions with proteus bacilli, but, like the viruses, they are intracellular parasites and have not been grown on lifeless media. Biologically not far removed from them is the psittacosis-group, whose members are commonly included in the viruses, they are the largest of the viruses, up to 300 m μ in diameter, are to some extent antigenically related to each other, seem to have a definite life-cycle within the cytoplasm of animal cells and are, many of them, unlike other viruses, susceptible to the therapeutic action of sulphonamides.

Constitution of Viruses

For a reasoned approach to the chemotherapy of virus diseases a knowledge of the constitution of viruses is essential. There is general agreement on the relative diameters of viruses, these lie between 10 and 300 m μ . It is also known that the shape of many viruses is very approximately spherical or ellipsoidal. There are great difficulties in obtaining such small particles in a state of purity, with the result that, although their chemical composition approximates to that of cells and bacteria, there is a dearth of exact knowledge on this matter. More is known of the chemical make-up of the viruses of vaccinia (Hoagland, Ward, Smadel & Rivers, 1942), influenza (Taylor, 1944), poliomyelitis (Gard, 1943, Loring & Schwerdt, 1942) and equine encephalomyelitis (Taylor, Sharp, Beard & Beard, 1943) than of the others, but each of these animal viruses may be described as a lipid nucleoprotein complex. On the other hand, according to Janssen (1941) the virus of foot-and-mouth disease is entirely protein. The plant viruses are, so far as is known, exclusively nucleoproteins. Though most of the known animal viruses contain lipoids as integral portions of their structure, that of rabbit papilloma is believed to consist wholly of nucleoprotein (Beard, Bryan & Wyckoff, 1939, Taylor, Beard, Sharp & Beard, 1942). The nucleic acids of the plant viruses are of ribonucleic acid

type, whereas those of animal viruses are either of ribonucleic acid or of desoxyribonucleic acid type. The presence of nucleic acid implies the presence of bound carbohydrate, but in influenza virus the carbohydrate content is greater than can be accounted for in combination in desoxyribonucleic acid (Taylor, 1944). It has also been found that the lipoids connected with viruses may include fats, phospholipids and cholesterol.

Vaccinia virus has phosphatase, catalase and lipase closely associated with it, but no dehydrogenases (Macfarlane & Salaman, 1938, Hoagland *et al.*, 1942), and is itself attacked by papain but not by trypsin, chymotrypsin, ribonuclease or carboxypeptidase (Hoagland, Lavin, Smadel & Rivers, 1940). On the other hand, a staphylococcal phage is attacked by chymotrypsin, but not by trypsin or pepsin (Northrop, 1938, 1939). Vaccinia has also been found to contain copper, and the fluorescence of vaccinia in ultra-violet rays led to the discovery of a flavine-adenine-nucleotide as a component in amount comparable with that in animal cells and some bacteria (Hoagland, Ward, Smadel & Rivers, 1941). As there is no evidence for the growth or metabolism of any virus in artificial media, the function of the constituents of viruses is not capable of direct investigation.

Chemotherapeutic Approach to Virus Diseases

If viruses consist largely of a lipid-nucleoprotein complex they should be vulnerable to attack. It is known that their activity is destroyed *in vitro* by many bacterial disinfectants and detergents, the latter probably bringing about the disintegration of the liponucleoproteins by setting free the lipoids, nucleic acids and proteins. The protein part is also amenable to attack by denaturants such as urea, guanidine, propylene glycol and potassium salicylate. Such methods of approach to a chemotherapy of virus diseases are however excluded by reason of the intracellular habitat of viruses. The whole difficulty of attacking agents such as viruses and rickettsiae with drugs lies in the facts that their sphere of activity is within the cell or even within the nucleus, and that their metabolism is very closely linked with that of the cell. Similar difficulties probably explain why serotherapy is so ineffective in virus diseases.

We do not know, however, whether a virus may not at times multiply within a limited number of cells, destroy them and, being liberated in the process, go on to invade more cells and destroy them in turn. If this happens, there is at least a possibility of sometimes catching the virus in the open and destroying it with a viricidal drug. It is possibly in some such way that measles antiserum, given during the incubation period of the disease, may suppress or modify its attack. A stimulation of the normal defence-mechanisms of the body against viruses, if it were possible, might be of value at an extracellular stage in the infection. It might also be possible to deny access of the virus to the cell by chemical modification of the cell's surface.

The main problem in the chemotherapy of virus diseases is, however, an attack on the viruses in their cellular environment. This could be a direct attack on the virus itself, or an attack on the sequence of processes involved in its multiplication. It is in the latter aspect that the greatest scope for interference lies. The problem is, however, one of the greatest difficulty, for the virus, having gained an entry into the cell, where dynamic conditions prevail, apparently mobilizes the anabolic processes of the cell for its own repro-

duction, and any selective disruption of this reproductive mechanism without at the same time harming the host-cell presents a formidable task.

What, therefore, are the possibilities of interfering with the reproduction of the virus in its intracellular habitat (Mudd, 1945)? The use of enzymes for bringing about the disintegration of the virus by a lytic action at any link in its structure is excluded in such an environment. Similarly the use of the usual laboratory lytic agents is out of the question. In fact, the only approach seems to be an attack on the "nascent virus". There are possibilities here. On the Woods Fildes hypothesis it should be possible to inhibit specifically the essential metabolites necessary for reproducing the virus structure by presenting to the cell chemical substances foreign to the cell but bearing a resemblance to the essential metabolites. In this connexion McKinstry & Reading (1944) have examined the effect of a large number of synthetic pyrimidines on the course of experimental poliomyelitis virus in mice, in the hope that compounds of this type might compete with the normal pyrimidine components of the virus for the synthetically-active enzyme systems. No unequivocal success could be recorded. The successful use of derivatives of sulphanilamide for combating infections with some members of the psittacosis group of viruses is, however, an excellent example of this principle of interference. Presumably *p*-aminobenzoic acid is necessary for the reproduction of this group of viruses, and is competitively inhibited by sulphanilamide or its derivatives.

Another possibility of interference is to present to the cell substances foreign to it, in the hope that they may be built up irreversibly into the structure of the virus with the production of something abnormal, in fact, a non-self-reproducing unit. That foreign substances can so be built up is instanced by the fact that wheat and corn grown on seleniferous soils produce proteins containing selenium bound in a form resembling the amino-acid cystine (Painter & Franke, 1935). Andrewes, King & Walker (1946a) have suggested that one interpretation of their finding that *p*-sulphonamidobenzamidine and *p*-sulphonamidobenzamidoxime have a therapeutic effect on an experimental infection of typhus in mice, would be to suppose that these amidines and amidoximes enter the cell and are built up, whilst nucleic acid synthesis is active, into some essential vital structure of the rickettsiae, this might well be through the amidine or amidoxime group, a group whose elements occur once in every pyrimidine and twice in every purine.

Another avenue of approach not covered by the foregoing, would be the discovery of chemical agents which would combine with the substances essential for virus reproduction, or with the enzymes which control the synthetic processes. In the latter connexion, many enzymes concerned in growth contain sulphhydryl groups, and it might be possible to block their activity selectively, claims to have achieved this in experimental poliomyelitis in mice with neoarsphenamine and other arsenicals are made by McKinstry & Reading (1945). The recent results of Fitzgerald and his colleagues (Fitzgerald & Babbitt, 1946, Fitzgerald & Lee, 1946) are also instructive. Several acridines, and particularly "phosphine GRN", were capable of inhibiting the reproduction of a coli bacteriophage at concentrations below the bacteriostatic end point. The anti-viral action was counteracted by ribonucleic acid, and the suggestion is made that the acridines inhibit the process involved in virus multiplication by competing for some substance related to

nucleic acid. The strongly-acidic phosphoric acid groups are salient features of nucleic acids and certain co-enzymes, and it is probable that they are the primary points of attachment of acridines and merit further experimental study *vis-à-vis* other types of bases with substantive character.

Another approach to the whole problem may come through an "interference phenomenon", which is, at any rate superficially, of quite a different nature. Many examples are now known in which infection of a host with one virus may suppress the activity of a second virus added together with, or even before, the "interfering" virus (Andrewes, 1944). Delbrück & Luria (1942) found that a bacterial virus (bacteriophage) inactivated by ultra-violet radiation could thus block the activity of living virus. Similar results were obtained by Henle & Henle (1943, 1944) and Ziegler & Horsfall (1944) for influenza, and by Andrewes & Elford (1946) for ectromelia virus. If the interfering principle, which seems to reside in the killed virus particles, could be isolated, chemically identified and perhaps imitated, new chemotherapeutic possibilities would be opened up. It might, however, be that an interfering agent was thus obtained, not so very different in its actions from those visualized in an earlier paragraph.

Results of Chemotherapeutic Trials

a Rickettsiae Though passing mention has been made of several of them, more detailed attention must now be given to such few successes as chemotherapy has already had in the field of rickettsiae and viruses. Activity against experimental typhus in mice has been found in the last few years in compounds of several unrelated groups of chemical substances. While the sulphonamides in the usual clinical sense seemed to do more harm than good, *p*-sulphonamidobenzamidine and the corresponding amidoxime were found to be active (Andrewes, King, van den Ende & Walker, 1944), closely-related compounds had lesser degrees of activity, but very little modification of the molecule was needed to abolish activity altogether.

The drugs had no *in vitro* action on the rickettsiae, possible mechanisms for their *in vivo* action are discussed by Andrewes, King & Walker (1946a). Their action was not inhibited by *p*-aminobenzoic acid. This latter substance has itself been claimed to have chemotherapeutic value against typhus both in man and in mice (Yeomans, Snyder, Murray, Zarafonets & Ecke, 1944). Activity against infection in mice has also been found in methylene-blue (Kikuth & Schilling, 1944), toluidine-blue and "forbisen" (Peterson, 1944), several dyes related to methylene-blue (Andrewes, King & Walker, 1946b) and penicillin (Moragues, Pinkerton & Greiff, 1944).

The dyes, unlike the compounds mentioned earlier, had a direct inactivating action on the rickettsiae, demonstrable *in vitro*. Activity of toluidine- and methylene-blue and of *p*-aminobenzoic acid has been shown against other rickettsial infections, those of rocky mountain spotted fever, and of scrub typhus (Hamilton, 1945, Murray, Zarafonets & Snyder, 1945, Anigstein & Bader, 1945). All these findings are at present of interest rather to the student of the theoretical aspects of the subject than to the practising clinician.

b Psittacosis group There is general agreement that a number of viruses in this group are susceptible to chemotherapeutic attack with sulphonamides or penicillin. Those of lymphogranuloma venereum and mouse-pneumonitis are readily attacked by a number of drugs in the sulphonamide group, though different authors place the various drugs in

different order of effectiveness (Findlay, 1940b, Jones, Rake & McKee, 1941, van den Ende & Lush, 1943, Felton, Hebb & Olphant, 1943). The substances prevent death from lymphogranuloma in mice, but rarely cause complete sterilization of the infection. Most workers agree that they have no *in vitro* killing action and are inhibited by *p*-amino-benzoic acid (MacCallum & Findlay, 1938, Levaditi & Perault, 1942, Rodaniche, 1943, Findlay, 1940a, Mudrow & Bock, 1943), but a few workers have put forward contrary views on these two points (Seeler, Graessle & Dusenber, 1943, Holder, Levine & Bullowa, 1942). Eaton & Hanford (1945) report very different activity on the part of sulphamerazine according to the host (mouse, hamster or chick embryo) in which the drug was tested. Some viruses of the group, when given intravenously in high concentration, kill within 36 hours by a so-called "toxic" effect. Such toxic deaths were not prevented by sulphonamides (Rake & Hamre, 1944).

Other viruses of this group, those of psittacosis, meningo-pneumonitis, and feline pneumonitis, seem to be unaffected by sulphonamides, but it is uncertain whether this will prove to apply to all strains, or whether there are strain differences in sensitivity to these drugs such as exist, for example, among streptococci. Trachoma and inclusion-conjunctivitis in man are held to be benefited by sulphonamides, here some part may be played by the action of the drugs on associated bacteria (Loe, 1938, Barrat, 1941). Heart-water of cattle responds to a sulphonamide, uleron (Neitz, 1940), though usually classed as a rickettsia (*R. ruminantium*), the agent of this disease is probably better placed with the group now under discussion. While not, or but rarely (cf. Bedson, 1943), affected by sulphonamides, the psittacosis virus can be attacked successfully with penicillin, at least in experimental infections (Heilman & Herrell, 1944, Parker & Diefendorf, 1944, Bedson & May, 1945), though it is likely that the dosage required is outside the limits practicable for man. Finally, Mauer (1938) has reported activity on the part of trypanflavin against psittacosis in mice.

c Action of sulphonamides on other viruses Claims have been made for activity on the part of various sulphonamides against influenza, lymphocytic choriomeningitis, dog distemper, measles and smallpox. These claims have failed of confirmation in the case of influenza virus and choriomeningitis infections. Activity in dog distemper (Marcus & Necheles, 1938, Bryan, 1941), measles (Hogarth, 1939, Anderson, 1939) and smallpox (Patel & Naidu, 1940, Cottrell & Knight, 1943, Leishman, 1944) is almost certainly due to an effect on the secondarily-invading organisms which are responsible for most of the complications and mortality. Evidence of action against the viruses themselves is lacking. Remarkable potency of sulphonamides against a virus

associated with fowl-paralysis has been reported by Asplin (1944), but no confirmation by other workers has appeared. *d Other chemotherapeutic studies in virus infections* Negative results of trials have been reported by numerous workers. Reference need be made only to those papers which report tests of considerable series of compounds on influenza (Coggeshall & Maier, 1942, Krueger *et al.*, 1943, Andrewes, King & van den Ende, 1943), on poliomyelitis (Coggeshall & Maier, 1942, Kramer, Geer & Szobel, 1944, McKinstry & Reading, 1944, 1945), on lymphogranuloma venereum (Andrewes, King & van den Ende, 1943), on St. Louis encephalitis (Kramer, Geer & Szobel, 1944), and on typhus (Andrewes, King, van den Ende & Walker, 1944), (see also van den Ende, Stuart-Harris, Fulton & Niven, 1946).

Of claims to have achieved success, few are based on strong evidence. Mention may be made, however, of reported activity of mercurochrome against canary-pox (Manwell & Goldstein, 1939, Coulston & Manwell, 1941) and of quinine against fowl-pox (Robbins, 1942). No attempt will be made here to review the numerous studies on *in vitro* action of many compounds on viruses, for it is questionable how far the results obtained are likely to find application in *in vivo* trials.

e "Chemotherapy" of bacteriophage A number of substances have been shown to be capable of suppressing the activity of a bacteriophage without greatly affecting the growth of the bacteria it attacks. While there is dispute as to how far analogies to infections with animal viruses may usefully be drawn from such studies, some of the results are of much interest and may possibly furnish useful clues. Stassano & de Beaufort (1925) and Bordet & Renaux (1928) found that some phages could be inhibited by dilutions of citrate and oxalate which did not affect the associated bacteria, the phage apparently needed more calcium ions for its growth than did the bacteria. According to Wahl (1946), certain phages require an optimum concentration of calcium for lysis, but lysis can be produced with less than the optimum amount of calcium ions if aneurin is added. Spizizen (1943) found that arsenite acted as a specific inhibitor of a coli-phage (γ). Reference has already been made to the work of Fitzgerald *et al.* (1946) on similar activity on the part of "phosphine GRN".

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Though the whole problem is a difficult one, there exist leads which are not without promise, of greatest encouragement is the fact that the rickettsiae and some of the larger viruses are susceptible to chemotherapeutic attack although they are, like the smaller viruses, strict parasites, closely dependent on the conditions existing within the cell for their life and growth.

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PRINCIPLES AND PRACTICE OF LOCAL CHEMOTHERAPY

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By some the word "chemotherapy" is confined to the use of substances having a systemic action, but by its literal meaning it should include the effective use of these and other substances by local application. Although the most notable advances of the past decade have been in the field of systemic treatment, there has also been a remarkable improvement in the results obtained by applying substances with an antibacterial action to the site of infection itself. Indeed, it is only within the last six years—a period almost coinciding, not without reason, with the World War—that this kind of treatment has been developed on rational lines. This change has been due in part to the introduction of new and more powerful antibacterial agents, but also to the employment

both of these and of older remedies in a more intelligent way. These advances have been connected mainly with the treatment of various kinds of wound, but infections in other parts of the body, such as the skin and various mucous membranes, have not been neglected.

PRINCIPLES

If local chemotherapy is to succeed, certain conditions must be fulfilled, and it is easy to illustrate failure due to lack of their observance by examples from the past. The chief of these conditions are the following

Adequate Antibacterial Action

It goes without saying that the substance employed should be capable, at least in favourable circumstances, of killing or at least of preventing the growth of the micro-organisms concerned. An example of a frequently-used wound antiseptic almost devoid of this power is iodoform. It is particularly interesting that this was the only wound antiseptic applied in the past in the form of a powder. This method has recently been recognized as having great advantages—provided, of course, that the substance so used has the necessary action—because it ensures persistence of effect.

It is often necessary to know the precise nature of an infection before deciding how to attack it, because the susceptibility of different micro-organisms to the same agent

may vary greatly. Generally speaking, the better the agent the more selective is its effect. Phenol is a weak germicide, but being simply a general protoplasmic poison, acts more or less equally on all bacteria. Acridines and dyes in general have a highly selective action, exerted mainly against gram-positive bacteria. The acme of selectivity is reached in penicillin, with an unexampled action on some bacterial species and less than none on others. I say less than none for two reasons: some bacteria are not only unaffected by penicillin but produce an enzyme which destroys it, secondly, there is some evidence that certain concentrations of penicillin actually stimulate the growth of bacteria resistant to it.

Efficacy in Body Fluids and Tissues

It is not enough that the agent used is lethal to bacteria in the test-tube, it must retain this power in the environment in which it is required to act in the body. This may be mucous secretion, faeces, blood, a serous effusion or pus. It is well recognized that many antiseptics fail on this account, magnificent performers in water, they lose all activity in a wound. This is due to chemical combination with some constituent of the medium, and is best illustrated by oxidizing agents such as hydrogen peroxide and potassium permanganate, and the halogens. Iodine and chlorine are both rapidly inactivated by body fluids, iodine, although an excellent skin disinfectant, is therefore not an efficient wound antiseptic.

The more modern local chemotherapeutic agents owe their success largely to the fact that such obstacles do not deter them. In the first full description of the properties of penicillin (Abraham, Gardner, Chain, Heatley, Fletcher, Jennings & Florey, 1941), experiments were described showing that its action on bacteria was exerted equally in broth, serum, blood and even pus. It seems likely that streptomycin will not prove equally indifferent to its environment. Abraham & Duthie (1946) have shown that its activity is much diminished in acid media. Since an acid reaction is often developed in foci of infection, the action of streptomycin may be hindered where it is most needed.

The Use of a Suitable Vehicle

This condition must be inserted because preparations have been used from which the active substance is not properly liberated. An extreme example of this is the old practice of dissolving phenol in olive oil, the resulting product was popular because it had none of the caustic action of a watery solution of the same strength. The explanation was simple: there was no caustic action because no phenol escaped from the oil, and for the same reason no effect on bacteria can have been exerted. The same objection applies, although not completely, to suspensions in liquid paraffin and other mineral-oil bases, these are generally less effective than watery solutions, although for some purposes they have other advantages.

Penicillin is frequently used in the form of an ointment or cream. It is important to know that the base is suitable. It must neither destroy the penicillin, nor retain it when the preparation is in contact with the tissues. Selbie, Simon & McIntosh (1945) have condemned a form of penicillin cream commonly used in Great Britain for failure to liberate penicillin freely, others have found this preparation more satisfactory.

Adequate Distribution

The agent used must be brought into contact with the whole of the infected area. In the treatment of superficial infections this presents no difficulty, in treating deep wounds or long sinuses, the difficulty may be insuperable. It is impossible, at least by ordinary methods, to disinfect a deep penetrating wound which has traversed muscle and fascia. Many wounds due to bullets and shell-fragments are of this nature, and it is therefore not surprising that applications to such wounds have often failed to prevent sepsis.

Adequate Persistence

All the most effective agents for local chemotherapy act slowly on bacteria. It is therefore necessary that they should be enabled to act for at least several hours and perhaps longer. This cannot often be achieved by the use of a solution, which was almost the only method used in the past. Antiseptics have often been used in so perfunctory a manner that only magical powers could have enabled them to have any effect. There has been a certain ritual which surgeons have been accustomed to perform, not unlike the rite of baptism, since the effect, if any, can only have been supernatural.

Two methods have largely superseded the use of solutions. One is the use of semi-solid preparations, with which a wound or other cavity is filled, after which it is covered with an occlusive dressing. Propamidine has been used in this way in the form of a jelly (Thrower & Valentine, 1943). Meleney's (1939) zinc peroxide paste is similarly applied, and a semi-solid cream of penicillin was successfully used by Florey & Williams (1944) for packing septic wounds of the fingers and hand. Perhaps the more important innovation is powder treatment. Here the agent is applied in solid form, and dissolves slowly in the exudate, thus maintaining an adequate concentration for some length of time. The first substance to be used in this way was iodoform, for the simple reason that it is almost completely insoluble in water, and hence could be used in no other way. Modern and effective powder treatment dates from the introduction of sulphonamides as local applications, which followed several years after their first use as systemic chemotherapeutic agents. Penicillin and acridine compounds (usually proflavine) have also been used in powder form, sometimes undiluted, but more often diluted with sulphanilamide or sulphathiazole.

The rate of solution of an agent used in this way is important. As Hawking (1941) showed experimentally, sulphanilamide is too soluble and sulphapyridine too insoluble for this purpose, one dissolves and disappears in too short a time, and much of the other may still be undissolved after several days. Sulphathiazole has an intermediate solubility and is thus more suitable, either alone or in combination with sulphanilamide, the latter giving a useful high initial concentration. It would be useful for this purpose if penicillin were a less soluble substance, proflavine (solubility 1 in 300) is ideal, persisting in adequate concentration for a long period.

Accessibility of the Infection

Local chemotherapy can be expected to succeed only in superficial infections, or in infection of cavities. If deep penetration of tissue is required, none but the systemic route is of any avail. It seems scarcely necessary to point this out, but gas gangrene was frequently treated in the past by the local application of hydrogen peroxide, than which

nothing could have been more futile. In this disease, the infection has spread into muscle many centimetres from the wound-cavity before the diagnosis is made. Inaccessibility may also result from loculation in cavities, and from the presence of sloughs, necrosed bone or other non-viable tissue.

Effect on Tissues

It is almost axiomatic that most ordinary antiseptics do as much damage to tissues as to bacteria. The ideal local chemotherapeutic agent should, as far as possible, be free from this disadvantage. The least toxic of all is penicillin, which has practically no ill effect on the cells of any tissue even in concentrations much higher than those which it is necessary to use. The sulphonamides are also comparatively harmless, but in concentrated solution they diminish cellular activity, and nervous tissue is particularly susceptible to damage by them. The least toxic of the older antiseptics are the acridine compounds, and although in concentrated form they cause actual necrosis of certain tissues, they can be so used as to obviate this effect. These are the three agents which have been chiefly used in the recent treatment of wounds.

PRACTICAL APPLICATION

1 Wound Prophylaxis

The prevention of wound sepsis is perhaps the most important of all forms of local chemotherapy. A clear distinction must be made between the prevention of wound infection and its treatment. For about two hours after the infliction of the wound, contaminating bacteria are still in the cavity of the wound, and have not begun to multiply and invade surrounding tissues. They are thus still relatively accessible, although those enmeshed in blood-clot, or situated in crevices between planes of tissue, are not likely to be killed by any application which has only a transient effect. No such application can take the place of necessary surgical treatment, foreign bodies and devitalized or grossly contaminated tissue must be removed.

The ineffectual attempts to prevent wound sepsis in the war of 1914-18 are now of only historical interest, their failure was due to delay in treatment, inadequate surgery, and the use of unsuitable agents, chiefly the older antiseptics with a high tissue-toxicity. The intelligent use of more effective agents dates from 1939.

Sulphonamides The powder treatment of wounds with sulphonamides was introduced by Jensen, Johnsrud & Nelson (1939) for the treatment of compound fractures in civilian practice. The method was widely employed for the initial treatment of battle-wounds in the war which began in that year. We have very little statistical information about its effect, although there is experimental evidence in plenty (Stephenson & Ross, 1940, Henderson & Gorer, 1940, Hawking, 1941, McIntosh & Selbie, 1942) of its efficacy under certain conditions in the prevention of gas gangrene.

Of its effect in preventing sepsis generally the clearest evidence is that collected by Bentley & Thomson (1945) among casualties during the battle for the Gothic Line in Italy. Their best results were obtained with penicillin, but in two other series of wounds, one treated with sulphanilamide, and one untreated by any form of local chemotherapy, the percentages becoming septic were 11 and 23 respectively. The percentages "infected" in the sense of containing pyogenic cocci without exhibiting signs of gross sepsis were 43 and 49, the authors conclude that sulphanilamide often

restrains bacterial activity sufficiently to prevent sepsis, but has little power of eradicating infection altogether. In the later stages of the war penicillin was used so extensively that further information about the action of sulphonamides alone has been scanty.

In blood or serous exudate the sulphonamides have a bacteriostatic action on pyogenic cocci and on some of the *Clostridia* and, provided that the powder is adequately distributed, and that solution and absorption are neither too rapid nor too slow, the multiplication of such bacteria must be restrained. If the method has been abandoned for some purposes, it is because even more effective methods are now available. The only serious evidence against its efficacy is the analysis of results in 2,191 civilian cases by Meleney (1945) according to which sulphonamide treatment, either systemic or local, did not reduce the frequency of infection at all. The discrepancy between these results and most others has yet to be explained.

Acridine compounds The subject of acute controversy since 1917, when they were first introduced, the acridine compounds have now found their proper place in wound treatment. Without reviewing their full history, it may be said that they owe their present recognition largely to the work of Albert and his colleagues, who have been indefatigable in synthesizing and studying the properties of new acridines, and in defining the conditions of their employment. It is due to their influence that acriflavine, which was largely used in earlier days, has been discarded, this substance is inconstant in composition, too toxic and too soluble. Proflavine, on the other hand, is a pure substance, of the ideal degree of solubility for persistent action when used in powder form, and less toxic. Perhaps the greatest influence of any single paper on this subject has been exerted by Russell & Falconer's (1941) observation that a buffered isotonic solution of proflavine is almost without toxic effect on an exceedingly vulnerable tissue, the exposed surface of the brain.

No one questions the antibacterial activity of the acridine compounds, their *in vitro* activity is very great and their capacity for preventing infection has been demonstrated repeatedly. They were found more effective than sulphonamides in two series of observations already quoted, those of Hawking (1941) and of McIntosh & Selbie (1942) on the prevention of gas gangrene. Recent controversy has centred chiefly on their toxicity when used in solid form. There is no doubt that proflavine powder in any considerable quantity will cause necrosis in normal tissues, Hawking (1943), Russell & Falconer (1943) and Russell & Beck (1944) have demonstrated this in various ways, using the powder either pure or diluted. Selbie & McIntosh (1943), on the other hand, consider that the changes produced by a powder containing 1 part of proflavine to 99 of sulphathiazole are not such as to contraindicate its clinical use. This mixture has been extensively used for the prevention of sepsis, and favourably reported on by McIntosh & Selbie (1944) and Ascroft (1944).

It was suggested by the writer (Garrod, 1940) that punctured wounds into which an antiseptic cannot easily be introduced might be treated by infiltrating the surrounding tissues with a solution of an acridine compound. This technique has been employed clinically by Arden (1945), using a 0.1% solution of 5-aminoacridine hydrochloride, without evidence of any undue toxic effect, the results in preventing sepsis were considered good.

Penicillin Against certain bacteria, penicillin is by far the

most powerful antiseptic known, and its absence of toxicity is another unique property. On the other hand, its free solubility is a drawback, since persistence following powder application is likely to be short. Penicillin became available in such vast quantities in the later stages of the war that nearly all our information about its power of preventing sepsis in wounds refers to parenteral treatment. It is nevertheless evident from the original studies of Florey & Cairns (1943) and from those of Bentley & Thomson (1945) that calcium penicillin, diluted with sulphanilamide or sulphathiazole, and used by insufflation, is a valuable prophylactic.

It is very desirable that further studies of the usefulness of penicillin-sulphonamide powders as wound prophylactics should be made. It has yet to be decided what is the best method of dealing with the various types of wound encountered in civilian practice, and present evidence suggests that such a powder is likely to be as effective as any other single application in preventing the development of infection.

2 The Treatment of Wound Sepsis

The treatment of a wound which is already suppurating is an entirely different problem from the foregoing. Large numbers of bacteria are present, in a different medium, and some are in the tissues bordering the wound. If the surrounding tissues are being invaded deeply, as in a spreading cellulitis or gas gangrene, local chemotherapy is of little value. The infection must be localized to the wound and, since it is usually suppurative, the chosen agent must be active in the presence of pus. That they are inactivated by tissue-breakdown products in pus is the reason for the relative uselessness of the sulphonamides for this purpose.

The acridines have no such disadvantage, and their successful modern use in septic wounds dates from the introduction of proflavine powder treatment by Mitchell & Buttle (1942). Granulation tissue is far more resistant than the normal tissues bordering a fresh wound to the toxic action of proflavine, and these authors introduced quantities up to 2 g. of the undiluted powder without ill effect, although amounts less than this were usually adequate. Wounds so treated dried up quickly and began to heal, even though suppuration had previously continued for months. This treatment has also been used successfully by Raven (1944) and by Heggie, Warnock & Nevin (1945). Mitchell & Buttle (1943) subsequently used diflavine (2,7-diaminoacridine monohydrochloride) in the same way with good results, and continuous irrigation with a solution of this compound or of 5-aminoacridine is recommended by Poate (1944). McIntosh, Robinson & Selbie (1945) report favourably on flavazole, a chemical compound of proflavine and sulphathiazole.

It is impossible here to review the many uses of penicillin in treating sepsis in various types of wound. Both powder insufflation and the instillation of a solution after suture were found by Florey & Cairns (1943) to control all gram-positive infection remarkably, at least in wounds not more than ten days old. Parenteral treatment has since very largely displaced these methods. How to treat septic conditions of the hand by locally-applied penicillin in the form of powder or paste is admirably described by Florey & Williams (1944). Provided that the infection is caused by penicillin-sensitive bacteria, that the whole area is accessible, and that persistence is achieved, this treatment is more successful than any other.

It is impossible to exaggerate the importance of technique in local penicillin therapy, progress has indeed consisted entirely of devising new methods of application for particular conditions. The chief aim of these has been to secure persistence of effect without repeated application. The latest example of these ingenious methods is that devised by Reading (1946) for mastoidectomy wounds. Florey & Florey (1943) originally suggested, for this purpose, suture of the wound and repeated instillation of penicillin solution through a tube. Reading fills the cavity with plasma in which penicillin has been dissolved, coagulates this by adding thrombin, closes the wound, and leaves it undisturbed until the sutures are removed. Primary healing resulted in 46 out of 50 cases. The plasma clot acts as a depot from which penicillin diffuses uniformly, presumably for as long as it is needed.

Penicillin is useless for "gram-negative" infection, due to such bacteria as *Proteus* and *Ps. pyocyanea*. These bacteria are also very resistant, although not completely so, to the acridines. Good effects on these infections have been claimed for ethylene glycol monophenyl ether (phenoxetol) (Berry, 1944, Gough, Berry & Still, 1944).

The place of cationic detergents in the treatment of wounds is still uncertain. They have a marked cleansing action, and probably have considerable prophylactic, although not much therapeutic, value. Examples are zephiran (Schumacker & Bethea, 1943), cetavlon (Barnes, 1942, Williams, Clayton-Cooper, Faulkner & Thomas, 1944) and phemeride (Iland, 1944).

3 Infections of Closed Cavities

The treatment of meningitis, empyema and suppurative arthritis has been revolutionized by the advent of penicillin. Provided that the infection is due to a penicillin-sensitive organism, the injection of penicillin solution into the infected cavity is the essential feature of the treatment. This is both far more effective and more economical than parenteral injection. The anatomy of the lesion fulfils one of the main conditions for success in local chemotherapy—that action shall be persistent. A single injection into such a cavity, where the solution is wholly retained and loss can result only from absorption, maintains its effect for many hours and, in the infected pleura, even for several days.

This form of treatment is applicable to meningitis, empyema, pericarditis, arthritis, and to abscesses in other situations such as the breast or connective tissue generally. It does not necessarily render ultimate evacuation of an empyema, or of the contents of an abscess elsewhere, unnecessary, even though the contents may be sterilized.

4 Skin Disease

Superficial bacterial infections of the skin offer a promising field for local chemotherapy, and a variety of applications used in the past probably had some such effect. They have now been largely replaced either by sulphonamides, which are undoubtedly effective, at least in impetigo, or by penicillin. There is now a considerable literature on the treatment of skin diseases with applications of penicillin in the form of a spray or cream, which it is not proposed to review here. The results can be summed up very briefly. When the primary cause of the disease is infection by staphylococci or streptococci, the treatment succeeds, when secondary infection by such organisms is present, there is improvement, when such infection plays no part in the disease, there is no

effect. The local treatment of blepharitis and conjunctivitis has also been highly successful when a penicillin sensitive infection is the cause

It is interesting that the conjunctival sac has been the site of almost the only example of chemoprophylaxis on which reliance has been placed throughout years of scepticism about antiseptics. The instillation of silver nitrate solution into the eyes of new-born infants has presumably prevented many cases of ophthalmia neonatorum. The time has come for this solution to be replaced by something less irritating and perhaps more effective. The application of penicillin cream to the eyelids would fulfil these requirements

5 The Respiratory Tract

The gargles, sprays, inhalations and lozenges of the past can have had extremely little effect. Not only were most of the antiseptics contained in them ineffective in themselves, but the method of application was much too transient. The factor of persistence is as important here as anywhere else, and none of these measures secured it. Effective local chemotherapy in the upper air passages began with the introduction by Delafield, Straker & Topley (1941) of sulphathiazole snuff for the treatment of nasal carrier-states. The slow solution of this powder in the nasal secretion was calculated to produce an effect lasting several hours. This treatment has been successfully used in treating carriers of *Staphylococcus aureus* and *C. diphtheriae*.

The more difficult problem of maintaining chemotherapeutic action in the mouth and tonsillar area was first solved by McGregor & Long (1944), who employed gelatin pastilles containing penicillin. These dissolved slowly, and patients were instructed to introduce another as soon as the previous one had disappeared, the effect could thus be maintained throughout the day. This treatment had a remarkable effect on Vincent's gingivitis, it was also valuable in preventing sepsis after dental extraction, compound fractures of the mandible, and tonsillectomy. It afforded some relief in acute streptococcal tonsillitis, and shortened the duration of the carrier-state thereafter. Recently Meadley & Barnard (1946) have advocated the treatment of acute streptococcal and Vincent's infection of the throat by the use of penicillin-sulphathiazole snuff. The medicament is carried through the naso-pharynx to the throat, which it

reaches within a few minutes, this was proved both by tests with dyes and by estimating the penicillin content of the oro-pharyngeal secretion, which usually remained therapeutically adequate for 3 hours after taking the snuff.

Finally, penicillin administered by inhalation has been used for the treatment of infections of the bronchi and lungs. This treatment is still in the experimental stage, and exact indications for it have not yet been defined. Marked, although temporary, benefit has been obtained even in bronchiectasis. The treatment of nasal sinusitis has been less successful, perhaps because adequate distribution and persistence cannot be achieved in the complex area involved.

COMMENT

This brief summary has dealt only with local chemotherapy by direct application. Urinary and intestinal antiseptics are in a somewhat different category, although they are in a sense examples of local chemotherapy, and have been the subject of great advances during the past few years. No reference has been made to antibiotics other than penicillin, although it is likely that in the future some of these will be found to have special indications. The most firmly established of these at present is tyrothricin. Suitable, owing to its systemic toxicity, only for local application, this substance has a variety of uses in the treatment of superficial infections, including wounds, ulcers, and infections of the eye and nose. Strange as it may seem, an antibiotic derived from a mould may yet prove to be a useful remedy for superficial mycoses, the studies of Sanders (1946) offer promise in this direction.

Advances in systemic chemotherapy have been the main feature of medical progress in the past ten years. One of their effects has been to revive interest in local chemotherapy. Surgeons and others who would not previously admit that antiseptics had any real value, faced with the spectacle of drugs which actually killed bacteria in the tissues and even in the blood-stream, were compelled to admit that a direct attack upon bacteria in some local and accessible site might also have some effect. The success of such proceedings has been due largely to the advent of new and better chemotherapeutic agents, notably penicillin, but it has depended also on observing principles which it has been the endeavour of this article to define.

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PRINCIPLES OF ADMINISTRATION IN CHEMOTHERAPY

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The successful use of drugs depends on maintaining an adequate concentration at the site of action for an adequate time. The achievement of this aim depends to a very considerable extent on the method of administration, the frequency of administration, and the use of a preparation dispensed in an appropriate form. In the past these matters have been left largely to chance. The therapist has decided what he considers is likely to be the best way of giving the drug, and if his results have been good his decision has been justified, but if his results have not been good, it has been difficult to know the reasons for his failure.

In recent years much more attention has been devoted to these matters. Different methods of administration have been controlled by estimates of the concentration of the active substances in the body and this has led to rapid advances. The new drugs which have been introduced recently would have been much less successful if their practical application had depended solely on the old empirical method of trial and error.

The problems involved in the study of the effects of different methods of administration are general pharmacological problems, and various different types of drug have been used in their study, but the present article is concerned primarily with chemotherapy and examples will be chosen, as far as possible, from experiments on drugs used against infections of various kinds. A fuller discussion has been given elsewhere (Gaddum, 1944a).

Methods of administration may be either systemic or local. When a systemic method is used the drug is intended to act after it has been absorbed into the blood-stream and distributed about the body. Such methods are used when the infection is widespread or when the site of infection is inaccessible. One advantage of local administration is that it is more economical, since smaller quantities of drug are generally used. It is also sometimes less dangerous, since high concentrations can be maintained locally which would have toxic effects in the body as a whole. It is also sometimes possible by local administration to reach parts of the body which are inaccessible to drugs given systemically, either because the circulation is poor or for other reasons. When the circulation is good where the drug is expected to act,

local administration is seldom effective because the drug is rapidly absorbed into the blood and carried away. In such cases the drug may act both systemically and locally and this may be an advantage, but the therapist should know what is happening, and for this reason it is sometimes desirable to estimate the drug in the blood even when it is applied locally near its site of action.

Excretion and Fate in the Body

The optimal frequency of dosing, or rate of administration, depends on the rate of disappearance of the drug from the site of action. This can seldom be measured directly. It depends partly on the rate at which the drug is destroyed locally and partly on the rate at which it is taken up by the blood or lymph or washed away in exudations or secretions. With systemic administration, satisfactory cures are usually obtained if an adequate concentration is maintained in the blood. The disappearance of the drug from the blood depends on the destruction of the drug, on its uptake by various tissues, and on its excretion in the urine, faeces, etc. The relative importance of these factors varies widely. Penicillin is mostly excreted in the urine, mepacrine is taken up by the tissues and slowly destroyed, only a small percentage appears in the urine. Ether is taken up by the tissues and then excreted unchanged. Acetylcholine is rapidly destroyed both in the tissues and in the blood itself.

The fate of a drug in the body can sometimes be followed by measuring the amounts in various organs and excreta, but it is seldom possible to account for the whole dose in this way. The simplest way of studying the relative importance of destruction and excretion is to eliminate complications due to the transference of the drug from one organ to another by making an extract of the whole animal. This type of experiment is most easily done with small animals such as mice or rats. Alexander (1943) carried out such experiments with sulphanilamide. Experiments on rabbits showed that this drug was first evenly distributed in the body-water and then concentrated in the liver, kidneys and urine, but a certain proportion of the dose could not be accounted for either in its original form or as the acetyl derivative. The suspicion that some of the drug had actually been destroyed was confirmed by estimations made on extracts of whole mice, which showed that 30% of the drug was destroyed and the rest was mostly excreted in the urine.

Frequency of Dosage • "Halving Time"

The curve showing the disappearance of drugs is often approximately exponential, the concentration falls rapidly at first and then gradually more and more slowly. The rate is conveniently measured by the half-disappearance time, or halving time, which is the time taken for the concentration to fall to half its initial value. When penicillin, diodone or *p*-aminohippuric acid is given intravenously, the halving time is measured in minutes. The halving time for sulphonamides or salicylates is measured in hours, for mepacrine or digitalis in days, and for suramin or mercury in weeks.

The frequency of dosing should generally not be less than the halving time if the concentration is to be kept fairly constant. The administration of larger doses at longer intervals may keep the concentration above the effective level, but is a comparatively wasteful way of using the drug, and is generally more liable to cause toxic effects. The more frequent the dosing, the more constant the concentration, but the greater the labour. The optimal frequency depends on a balance of these two factors. Continuous administration is ideal both for economy of drug and constancy of concentration. It can be achieved by an apparatus which produces a steady flow of solution or by the more or less steady liberation of the drug from a more or less insoluble depot. Examples of these techniques, both for systemic and local administration, will be given later.

Devices which slow the disappearance of a drug have two advantages. They decrease the amount needed and make it easier to attain a steady concentration. The appropriate method depends on the mode of disappearance. Acetylcholine is destroyed by cholinesterase, and its disappearance can be slowed by giving eserine, which inhibits this enzyme. When a drug is excreted in the urine, its disappearance can sometimes be delayed by slowing the excretion. The great speed at which penicillin appears in the urine proves that it is actively excreted by the tubules. Its disappearance can be slowed by giving other drugs which are excreted in the same way, and so overload the excretory mechanism. Both diodone (Rammekamp & Bradley, 1943) and *p*-aminohippuric acid (Beyer, Woodward, Peters, Verwey & Mattis, 1944) have this effect.

When a drug is given continuously, or in frequent small doses, it gradually accumulates in the body, and the half-accumulation time is equal to the half-disappearance time (Gaddum, 1944b). When the halving time is short, as with penicillin, the concentration rapidly rises to the desired level, but when the halving time is longer the concentration may rise too slowly, and it is necessary to give large doses at first and then reduce the rate of administration when the effective concentration is attained. This technique is used with digitalis, salicylates, mepacrine, sulphonamides and many other drugs which are given systemically. It is not commonly used for local applications, because in this case the halving time is generally short.

The dose necessary to produce a given initial concentration in the blood depends on the volume of distribution. The dye T1824, or Evans blue, is used to measure the plasma-volume, which is equal to its volume of distribution. With chlorides, bromides and thiocyanates the volume of distribution is roughly equal to that of the extra-cellular fluid. Many substances, such as alcohol, urea or sulphanilamide, are evenly distributed in all the body-water. Some drugs, such as mepacrine, are rapidly concentrated in certain tissues, and the apparent volume of distribution is much larger than the total volume of the body. The importance of these facts is mainly theoretical, and the appropriate initial dose is determined empirically.

Oral Administration

The simplest way of taking drugs is to swallow them, and this is the method of choice when it is effective, but many drugs are poorly absorbed or destroyed before absorption. Absorption through the oral mucous membrane is slow and, although some drugs have systemic effects when given in lozenges or pastilles to be placed under the tongue, this

technique is mainly used for its local effect in the mouth. For example, penicillin pastilles have given encouraging results in the treatment of Vincent's angina (MacGregor & Long, 1944). Few drugs, except alcohol, are appreciably absorbed in the stomach, and absorption from the rectum is also slow and erratic. The main site of absorption is the small intestine, and various devices have been used to get unstable drugs into the duodenum before they are inactivated in the stomach. The devices that have been tried include duodenal tubes, which are effective but laborious, the administration of alkalis to neutralize the gastric juice, and the use of insoluble preparations or of tablets coated with insoluble materials such as salol, stearic acid, keratin, or gelatin hardened with formalin. Cellulose acetate phthalate has recently been recommended for this purpose. It is soluble in alkalis but not in acids, and experiments with *x* rays and capsules containing barium sulphate showed that disintegration occurred in the small intestine (Hodge, Forsyth & Ramsey, 1943). Such preparations are best given on an empty stomach with a drink of water, so that they pass quickly through the pylorus.

Absorption from the intestine is seldom a very rapid process and drugs given in this way have a more prolonged action than when they are injected. Attempts to prolong their action by the use of insoluble preparations are limited by the fact that drugs which are not absorbed fairly rapidly are apt to be lost through the anus. Various sulphonamide derivatives are comparatively slowly absorbed and have been used to disinfect the lumen of the intestine. They are extremely effective for this purpose and liable to cause vitamin deficiencies in the patient by inhibiting organisms which form vitamins in his gut. The reasons for their slow absorption are uncertain, they are not all of them particularly insoluble. It is possible that the slowness of absorption of these drugs is due to the fact that they are not ionized (Krebs & Speakman, 1946). On the other hand, it is possible that light will be thrown on this problem by experiments of the type carried out by Bose, Ghosh & Rakshit (1946), who injected various sulphonamides and then estimated their concentrations in the contents of the alimentary canal. Those concentrations were sometimes much higher than the concentrations in the blood. The best drug for disinfecting the gut may be the one which is most actively excreted into the gut. On the other hand, Hawking (1942) obtained evidence that very little sulphaguanidine is excreted into the gut compared with the amounts in the urine. Further evidence is desirable on this point.

Intravenous Injection

Intravenous injections are used to get a quick action, or when the solution is irritant. Rapid dilution by the blood diminishes the irritant effects, though very irritant solutions may cause local phlebitis. If the solution is injected very rapidly the drug may all reach the heart and lungs almost undiluted and cause immediate toxic effects upon them. If a minute or two is taken over the injection, this particular danger is generally avoided, but even then the concentration in the blood as a whole may rise to dangerous levels before the drug passes to the tissues. The dangers of "speed shock" were emphasized by Hirschfeld, Hyman & Wanger (1931). This led to the administration of neoarsphenamine, and later mapharside, by slow intravenous infusion (Hyman, 1940).

The rate of disappearance is usually high when drugs are given intravenously, so that slow, rather than quick, injection is advisable, not only because it is less likely to cause toxic effects, but also because it is more likely to maintain an effective concentration in the blood for an adequate time. Such infusions may have to be maintained for a number of days. Special needles have been devised which can be kept in position on a patient's arm and which give him some freedom of movement (Herrell, 1945), but some workers have had poor results with needles and prefer to tie a cannula in a vein. This technique has the disadvantage that when the cannula is removed the vein must be tied and cannot be used again. In any case the vein usually becomes inflamed after a few days and the site of injection must then be changed. The number of available veins is large but not infinite.

The fluid should contain isotonic sodium chloride (1%) or glucose (5%). Various workers have proposed that heparin should be added to prevent thrombosis (Martin, 1944). A common rate of injection is 2.5 cm³ per minute or 3.6 l in 24 hours. The apparatus is usually a simple reservoir 2 feet [0.6 m] above the patient, and the rate is controlled by a screw-clip and a drip-feed.

Marrow Infusions

The administration of fluids into the bone-marrow was first described by Tocantins & O'Neill (1941). Such fluids pass directly into the blood-stream, and even blood itself can be given in this way. The rate may be as high as 25 cm³ per minute, and this method has been recommended as easy, quick and safe when veins are difficult to find (Bailey, 1944; Morgan, Christie & Roxburgh, 1944). The infusion of penicillin into the marrow near the site of osteomyelitis should be particularly effective by producing a high local concentration as well as an adequate concentration in the systemic blood (Aird, 1945).

Subcutaneous and Intramuscular Injections

These have the advantage of simplicity, the needle can be inserted by a nurse. Fluids may be given either continuously or in repeated doses. For continuous administration the intramuscular method is best, since absorption is quicker. Using two needles in the thigh muscles, fluids can be given as rapidly as 5 litres in 24 hours, or 3.5 cm³ per minute (Billimoria & Dunlop, 1940), but high rates are liable to cause pain, and it is generally agreed that the volume given by this route in 24 hours should be as small as possible. The slower the rate of injection the more difficult it is to get a steady flow, and various devices have been used for this purpose. One simple apparatus which delivers 100 cm³ in 24 hours is known as Eudrip III (McAdam, Duguid & Challinor, 1944), the rate is controlled by the flow of air through a capillary tube. Various authors have described electrically-operated machines which gradually push in the piston of a syringe. In this way the rate may be reduced to as low as 2 cm³ per 24 hours. The need for economy in the use of penicillin has been a potent stimulus to the invention of such methods of administration. Now that penicillin is becoming more plentiful, there is a tendency to revert to the simpler procedure of repeated injections.

When repeated injections are used it is usually an advantage if the drug is slowly absorbed so that a fairly steady concentration is maintained in the blood. There are many methods of forming such depots of drug, and some of them are apt to be too effective, so that an adequate concentration in the

blood is never reached. The route of absorption depends on the molecular weight of the substance absorbed. When this is greater than 20,000 (which is about that of the smallest protein molecules), absorption is by lymphatics and can be slowed by immobilizing the site of injection. Smaller molecules are absorbed by the blood (Barnes & Trueta, 1941).

The rate of absorption depends on a number of factors

i *Site of injection* Intramuscular injections are usually absorbed more quickly than subcutaneous injections

ii *Local circulation* Warmth dilates the blood-vessels and quickens absorption, and cold has the opposite effects. Trumper & Hutter (1944) have recommended that the site of injection of penicillin should be chilled to slow absorption and diminish pain. The circulation can also be slowed by adding a vasoconstrictor such as adrenaline to the injection and this method is used to delay the absorption of local anaesthetics.

iii *Surface-area of the depot* A watery solution of a bismuth salt is absorbed more rapidly than an oily solution, partly because it is less viscous and spreads more widely in the tissues. The effect of the surface-area is also shown particularly clearly when pellets of steroid hormones are implanted subcutaneously. Such pellets may continue to be absorbed for many months (Thorn, Dorrance & Day, 1942; Dunlop, 1943). They can be taken out at intervals and weighed and measured. In this way it has been found that the rate of absorption is directly proportional to the surface-area (Bishop & Folley, 1944).

iv *Solubility of the drug and its vehicle in the tissue fluids* This is the most important factor, and there are many ways of taking advantage of it. The solubility of the drug can be controlled by converting it into a salt with the appropriate properties. Experiments with steroid hormones have shown that this has a marked effect on the rate of absorption. The solubility of the vehicle can also be controlled. Drugs may be given suspended or dissolved in water or in fatty oil. Protamine-insulin is a relatively insoluble preparation which is injected in watery suspension. Globin insulin and bismuth tartrate are injected in watery solution, but are immediately precipitated in the tissues and then slowly dissolved. Propylene glycol can be used in much the same way. It is readily miscible with water, but dissolves steroid hormones and other fat-soluble substances. When such solutions are injected the solvent mixes with the tissue-fluids and the drug is precipitated and then slowly dissolved. Water-soluble substances such as adrenaline (Kennedy, 1941) or pitressin tannate (Court & Taylor, 1943) or sodium penicillin (Raiziss, 1944) are slowly absorbed when injected in suspension in oil, but oils are more commonly used for drugs which dissolve in them.

When liquid fats such as peanut (arachis) oil or sesame oil, or esters such as ethyl oleate, are injected intramuscularly, they and the drug are slowly absorbed. The rates of absorption and local irritant effects of various oils have been studied by Brown, Wilder & Schwartz (1944), who came to the conclusion that sesame oil and maize oil were preferable to cottonseed oil and peanut oil. The rate of absorption of these oils can be slowed by adding substances such as beeswax, which consists of long-chain alcohols and fatty acids and their esters. It is relatively insoluble in water and diminishes the solubility of the oil. It has been used to delay the absorption of histamine, desoxycorticosterone acetate, heparin, and penicillin (Romansky & Rittman, 1944).

Respiratory Tract

The mucous membrane of the nose is a fairly effective absorbing surface, and snuffs containing nicotine, cocaine or heroin give satisfaction when applied to it. Pituitary extracts have been given by this route, but the method is not very reliable. Drugs applied to the nose are usually intended to have local effects, but if large quantities of oil are given in this way as a solvent, it may run down into the lungs and cause pneumonia (Robertson, 1940).

Sprays are sometimes used to administer drugs to the lungs. The simplest forms of spray produce large drops which are deposited in the nose. It is only droplets with a diameter of $5\ \mu$ or less which reach the lungs, and these form a stable cloud which shows no tendency to settle. Such clouds are produced by sprays containing a baffle, which returns all but the smallest drops to the input of the spray (Collison, 1935). Water-soluble substances which reach the lungs are very rapidly absorbed into the general circulation, and a lung may absorb several times its own weight of water in an hour. On the other hand, it is difficult to give much drug in this way. The total weight of the drops in a cloud is commonly about 5-10 mg per litre. If, therefore, it is possible to use a 10% solution of the drug and to induce the patient to inhale 10 litres per minute and retain all the drops, he will receive about 5-10 mg of drug per minute. Usually the rate of administration will be less than this, and prolonged inhalation will be necessary to get much drug into the systemic circulation.

On the other hand, such sprays produce a high concentration of the drug on the walls of the bronchi, and it is not difficult to produce effective concentrations of drugs in the sputum. This method of administration is thus most likely to be effective in the treatment of infections of the bronchi. Both sulphonamides (Mutch, 1944) and penicillin (Bryson, Sansome & Laskin, 1944) can be used in this way.

Serous Cavities

The permeability of the linings of the body-cavities is important in the treatment of infections of these cavities. The sulphonamides usually penetrate serous membranes easily, but penicillin normally does not do so and is often given by local injection. When the membrane is inflamed its permeability in both directions is increased. Systemic administration is therefore likely to be more effective in the treatment of infections of the pleura, meninges and joints than might be expected from experiments on normal subjects. The peritoneum is more permeable than other membranes. Penicillin is given by injection into the pleural cavity, joints, and cerebrospinal fluid in the treatment of local infections of these parts, and an effective concentration is usually obtained for much longer than would have been the case if the same dose had been given systemically. It must be remembered, however, that such infections usually involve the tissues surrounding the cavity as well as the fluid inside, and it is often desirable, therefore, to maintain an effective concentration in the blood as well as in the cavity. When sufficient penicillin is injected locally in such cases, it may actually increase the blood-concentration effectively for long periods through slow absorption of the drug. It has even been suggested that penicillin should be injected into normal cavities in order to treat infections elsewhere, but the rate of absorption is not likely to be under good control in these circumstances, and it is doubtful whether this method of forming a depot will have wide application.

Wounds and Burns

The application of drugs to wounds has been discussed by Robson (1943) and Hawking (1943). In parts of a wound where the circulation is good, the local administration of drugs is unlikely to be effective because the drug is rapidly absorbed, and systemic administration is more likely to achieve results. Where the circulation is bad, the only effective way of using drugs is to apply them locally. Drugs diffuse very slowly over distances of 1 cm or more unless they are carried by convection currents, and it is therefore necessary to ensure that the method of application carries the drug to all parts of the wound. Dead tissues form a barrier to drugs, and their removal is therefore desirable for this reason as well as others.

Drugs are liable to disappear rapidly from wounds, either because they are absorbed or because they are inactivated. It is therefore usually necessary to apply the drug continuously or repeatedly, or to form a local depot from which the drug is slowly liberated. The continuous irrigation of wounds has been much used, and is particularly likely to be effective when the wound is enclosed in a bag through which a solution of the drug runs. Penicillin is effective when given intermittently through a rubber tube inserted through the skin when a wound is sewn up. Local depots can be formed by the use of powders which are sprinkled or insufflated over the wound and as far as possible into crevices. The concentration of the drug in the wound then depends on its solubility. Sulphanilamide is fairly soluble and effective. Its rate of absorption is very roughly half its rate of absorption from the intestine (Hawking, 1943), and it may therefore cause general toxic effects if excessive quantities are used. Many other sulphonamides are relatively insoluble, and are effective only when a very fine powder is used.

Drugs may also be applied as creams particularly in the treatment of burns (Robson & Wallace, 1941; Colebrook, Clark, Gibson & Todd, 1944). The use of sprays is convenient, but drugs applied in watery solution in sprays are liable to be quickly absorbed. When the drug is incorporated in dressings it is not likely to reach deeper parts of wounds.

Eyes

Drugs do not pass readily from the blood-stream into those ocular tissues which have a poor blood-supply, they are therefore often applied locally. The application of a 30% solution of sodium sulphacetamide to the surface of the conjunctiva is effective in the treatment of corneal ulcers (Robson & Scott, 1941). This particular sulphonamide was chosen because it is very soluble at neutral pH. Penicillin is also effective when used in the same way. Under suitable conditions, drugs penetrate to the cornea, sclera, aqueous humour and iris. The main barrier to penetration is the epithelium on the surface of the cornea (Ginsburg & Robson, 1945). The penetration of local anaesthetics through this epithelium is increased if the solution is alkaline, since the free base penetrates more readily than ions. Wetting-agents also increase the penetration of sulphonamides, but not of penicillin, by destroying the epithelium. When given in drops, the drug disappears rapidly, and hourly administration is recommended. The labour involved in such frequent application can be avoided to some extent by the use of cotton packs soaked in the drug or a corneal bath. A more effective method is to inject the drug subconjunctivally or into the aqueous or vitreous humour (Brown, 1946).

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¹ [See BMB 719/127]

² [See BMB 318]

History

934

The important contributions of France to chemotherapy have received relatively little attention in some of the relevant literature. The article below was contributed by invitation, and is a first-hand account of the chemotherapeutic work of the Institut Pasteur. It has been placed for convenience in our Historical Section, although the Institut Pasteur is essentially a part of the medical history, not of the past, but of our own time.

THE CONTRIBUTION OF THE INSTITUT PASTEUR, PARIS, TO RECENT ADVANCES IN MICROBIAL AND FUNCTIONAL CHEMOTHERAPY*

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Protozoa and Spirochaetes

1 Trypanosomiasis

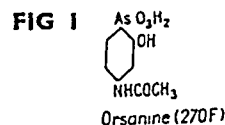
At the Institut Pasteur in 1902, Laveran and Mesnil¹ established the conditions necessary for transmitting trypanosomiasis from one animal to another. Mesnil and Nicolle² in their later studies of this disease demonstrated the therapeutic properties of certain dyes, such as afridol

* Translated from the French by A H S with assistance from Dr F R Selbie

violet and trypan blue, and also of several arsenical compounds

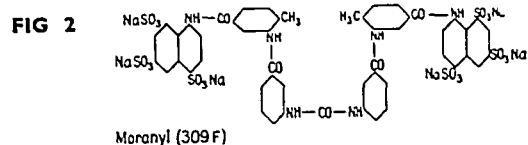
The study of the latter group of compounds was continued by Ernest Fournau, who is justly considered to be the successor of Ehrlich, the pioneer of chemotherapy. Fournau, appointed director of the Department of Therapeutic Chemistry at the Institut Pasteur in 1911, contributed to the identification of atoxyl, the first active drug that could be used with safety in the treatment of human and animal trypanosomiasis.

The exact determination of the structural formula of atoxyl has had a decisive effect on further research on the arsenical drugs. Once it was known that atoxyl was not an arsenical salt of aniline but that the arsenic was directly attached to the benzene ring, it was possible to change the position of the amino group, or the group itself could be altered, replaced or supplemented by other groups. It is the study of derivatives obtained in this manner which we have pursued, especially since 1921, in the Laboratory of Therapeutic Chemistry, and which led us to the demonstration of the chemotherapeutic properties of orsanine and stovarsol¹.



Orsanine (Fournau 270) (Fig 1) is the remedy for the first stage and the beginning of the second stage of sleeping sickness, as the American tryparsamide is for the final stage of this disease. Moreover, treatment with a combination of orsanine and moranyl is an example of true synergy, since the latter re-sensitizes trypanosomes which have become resistant to the action of arsenical drugs. The history of moranyl (Fournau 309) (Fig 2) is worth recording. The formula of this substance is identical with that of germanin (Bayer 205),

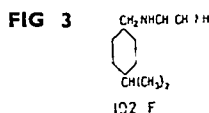
which the Germans refused to disclose when tests were being carried out in Africa. Bayer 205 has an exceptionally high therapeutic index in mice, the toxic dose being more than 300 times greater than the therapeutically active dose. The first results in man were so promising that the Germans



offered to hand over the formula of Bayer 205 in exchange for the Cameroons. Fourneau, Trefouel, Trefouel and Vallée⁴, however, were fortunate enough to discover the formula of this substance and published it at once. They also demonstrated the amazing specificity of its trypanocidal properties in fact, by simply removing the CH₃ group or transferring it from the first to the second benzene ring, it was possible to cause a decrease, or even complete disappearance, of activity.

Fourneau, Trefouël, Tréfouel, Bovet and Koetschet⁵ showed later that the polyarsenical derivatives have a selective action on *Trypanosoma congolense*, whereas the mono-arsenical derivatives are totally inactive.

Before leaving the field of trypanosomiasis, mention should be made of the work of Funke and his co-workers⁶, who demonstrated the trypanocidal properties of Fourneau

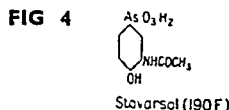


1921 (Fig 3), the most active member of a series of diamines that had no relationship to any of the previously known series of trypanocides. Fourneau 1921 is active whether it is given subcutaneously or orally.

ii Spirochaetal infections

The activity of bismuth in syphilis was first discovered at the Institut Pasteur by Sazerac and Levaditi in 1922.⁷ Bismuth still plays an important part in the therapy of this disease along with mercury, arsenic and penicillin.

In the course of our study of the arsenical acids we found in stovarsol (Fourneau 190) (Fig 4) another striking example of



the interdependence of therapeutic properties and chemical constitution. Examination of its formula shows that it differs from orsanine only in the position of the groups NHCOCH₃ and OH in relation to the arsenic acid group. And yet, while orsanine is the specific for sleeping sickness, stovarsol is the specific for the spirochaetal infections, syphilis and yaws.^{8,9} It is active by mouth and gives excellent

results in natural and experimental tertiary syphilis. It is also active against certain intestinal parasites (*Giardia lamblia*, amoebae¹⁰, *Blastocystis hominis*) and *Plasmodium vivax*.¹¹

iii Malaria

About 1928 Fourneau's team opened a new research laboratory for the study of synthetic antimalarial drugs in the canary and Java sparrow [*Padda oryzivora*]. In the series of quinolines with a carbon-nitrogen side-chain we have found some interesting relationships between chemical constitution and activity against various forms of plasmodia.¹² In particular, we have shown that with progressive lengthening of the carbon side-chain there is a diminution of activity on gametes, whereas the effect on schizonts is non-existent with the shorter carbon chains and gradually increases, as the side-chain is lengthened, to become quite definite with the group C₁₁ (Fourneau 852) (Fig 5, 6) of which the stovarsol salt is Fourneau 915.

FIG 5

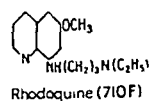
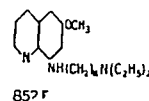


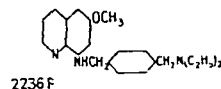
FIG 6



This represents the logical link uniting the series of plasmoquin, the gametocide, to that of quinine, the schizonticide. The first clinical tests were carried out by Marchoux and Chorine.¹³

Funke, Bovet and Montezin¹⁴ have studied the effect of interpolating an aromatic nucleus in the carbon chain.

FIG 7



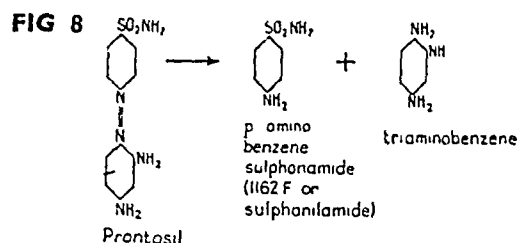
Among the substances tested, Fourneau 2236 (Fig 7) showed a characteristic antimalarial activity against experimental avian infection (canaries, fowls). Its relatively low toxicity for animals justifies its clinical trial.

Bacteria and Filtrable Viruses

i Sulphonamides

The development of antibacterial chemotherapy dates from 1935, when Domagk¹⁵ demonstrated the antistreptococcal properties of prontosil. We immediately commenced a study of prontosil derivatives, applying the chemical and biological principles that had proved their value in anti-protozoal chemotherapy. In a very short time we discovered that the usual rule of specificity of action was no longer valid for this series, at least in so far as changes in the second nucleus of prontosil were concerned, since none of these affected antibacterial activity. We thought it logical to assume that this second nucleus played only a secondary therapeutic role, if any, on the other hand, knowing that the azo linkage is relatively weak, we put forward the conception that prontosil, under the influence of constant oxidation-reduction reactions in the body, would be split at the link -N=N- by the acquisition of hydrogen and the

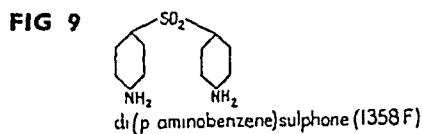
liberation of two independent molecules, that of *p*-aminobenzenesulphonamide from the first nucleus and that of triaminobenzene from the second nucleus of prontosil (Fig 8)



As this second nucleus did not seem to play any part in therapeutic activity, we prepared *p*-aminobenzenesulphonamide (Fournau 1162 or sulphanilamide), which Gelmo had prepared as early as 1908, and carried out tests with it on mice. The first results were conclusive, showing that streptococcal infection in mice was no more resistant to sulphanilamide than to prontosil and was, in fact, more sensitive to the new drug¹⁶. This observation solved the apparent paradox of the complete inactivity of prontosil *in vitro* compared with its activity *in vivo*. In fact, prontosil cannot act *in vitro* since it retains its identity, it becomes active only when it is transformed by the animal organism into sulphanilamide, which is active both *in vitro* and *in vivo*. From then onwards, the study of the azo-derivatives was completely abandoned, and sulphanilamide became the starting-point for further research by bacteriologists and chemists.

We then showed¹⁷ that sulphur could manifest its activity in other forms than that of the sulphonamido group $-\text{SO}_2\text{NH}_2$. Activity increases with the degree of sulphur oxidation, and we have been able to classify sulphur-derivatives in order of interest as follows: sulphides, sulfoxides, sulphones.

Of all the substances we have tested, di(*p*-aminobenzene)sulphone (Fournau 1358) (Fig 9) is the most active against



streptococcal and pneumococcal infections in the mouse. Our friend Dr. Buttle reached an identical conclusion at the same time as we did. But Fournau 1358 is extremely toxic and shows no evidence of the exceptionally wide range of activity displayed by sulphanilamide. Rodilone (Fournau 1399) can be obtained by means of diacetylation.

By means of experiments on *Aspergillus niger* we were able in 1936 to outline the mode of action of sulphanilamide¹⁸ and to conclude that it does not exert an antiseptic action, but simply one of bacteriostatic inhibition. It "suspends life". The recent experiments of Lwoff and others¹⁹ on a flagellate of fairly large size, *Polytomella caeca*, allow us to follow this mode of action with ease: after two or three normal divisions, flagellates of considerably increased size are obtained, these are unable to multiply, but their vitality is completely preserved, since they again divide normally after the addition of an antsulphonamide, such as *p*-aminobenzoic acid. These experiments have, moreover, shown that the relative activities of sulphanilamide and *p*-aminobenzoic acid are determined by cell-permeability, the maximum bacterio-

static activity being at pH 7, and the maximum antsulphonamide activity being at the isoelectric point of pH 3.8.

Nitti and others²⁰ have investigated the production of antsulphonamides in culture media: they confirmed that antsulphonamide activity accumulates in the most degraded protein fractions, and tested the activity of some of the amino-acids that constitute the final products of the protein degradation scale: two of these, *dl*-leucine and *dl*-methionine, manifested some activity, but this was inferior to that of *p*-aminobenzoic acid. The same authors have also synthesized a mixture closely resembling a final hydrolysate of myosin, and have been able to show that this mixture, which is inactive by itself, has a definitely stimulating effect on the activity of *p*-aminobenzoic acid, possibly this results from an increase in the ability of the bacteria to produce *p*-aminobenzoic acid. Finally, these authors have shown that the comparative antsulphonamide activity of peptones and of *p*-aminobenzoic acid varies with the nature of the bacteria: cultures of *Proteus*, *B. coli*, and Friedlander's bacillus that are inhibited by sulphanilamide resume growth equally well with the addition of either *p*-aminobenzoic acid or peptone, whereas with cultures of streptococci and pneumococci growth is re-stimulated by *p*-aminobenzoic acid but not by peptone.

Our knowledge of the antsulphonamide factors in peptone media led to a better understanding of the local use of sulphonamides in the treatment of wounds by showing that sulphanilamide inhibits the development of streptococci and *Cl. welchii*, which were together responsible for 75% of the deaths in the 1914-18 war, the experimental investigations of Legroux and Nitti²¹ on guinea-pigs and rabbits made possible the treatment of the war-wounded in the spring of 1940.

The sensitivity of a micro-organism to sulphonamides depends not only on its nature, but also on its virulence. This was shown by Nitti and Bovet²²: microbes of low virulence give rise to infections which are much more difficult to suppress, on the other hand, when microbes suspended in mucin are injected, their virulence is increased and chemotherapy once again becomes effective.

Another factor which influences the action of drugs is the development of resistance to chemotherapy in certain micro-organisms. Roux and Cheve²³ have shown that strains of meningococci can be trained to withstand increasing concentrations of sulphanilamide and sulphapyridine. But, whereas in the first case virulence is reduced, the strains rendered resistant to sulphapyridine have retained their virulence and can cause infections in mice that are refractory to treatment not only with sulphapyridine but also with sulphanilamide.

In order to render sulphanilamide active against the staphylococcus in cases of furunculosis or carbuncle in which vascularization is deficient, Legroux had the idea of combining sulphonamide treatment with the resolvent properties of iodine, iodine softens the nodular lesions and thus allows sulphanilamide to exert its action on the originally encysted staphylococci²⁴.

The first clinical experiments with Fournau 1162 (sulphanilamide) were carried out at the Hôpital de l'Institut Pasteur by Martin and Delaunay²⁵. In the course of the following years, Martin and his co-workers²⁶ established the principles of dosage and methods of estimation which made the use of sulphonamides possible in France with the maximum safety and efficiency.

ii Penicillin

It was this same team that was the first in France to experiment with penicillin during the occupation years. Thanks to the combined efforts of the Rhone-Poulenc Company and F. Nitti, a small quantity of penicillin was prepared and the first cases treated with this drug date from 1944³⁷. Later, our hospital was among the first to receive penicillin from England and America, and this made it possible to extend the original results³⁸.

In order to increase our stock still further, we established in March 1945 a laboratory for the recovery of penicillin from the urine of patients undergoing treatment³⁹.

The laboratory for the estimation of penicillin added to previously known techniques by perfecting A. Prevot's method⁴⁰, which was based on an entirely new principle: the test organism, *Cl. welchii* or *Cl. butyricum*, decolorizes Janus green by means of reduction in about an hour, and if the amount of penicillin present is sufficient to inhibit the growth of these bacteria, there is no decolorization. The method is sensitive and rapid, giving results in about 2 hours.

We have already said that Nitti was in possession of penicillin in 1944. With the aid of the microbiophotometer, which was constructed by Faguet and Nitti⁴¹, and registers bacterial growth-curves, it was possible to demonstrate the mode of action of penicillin: in the first stage, lasting 2-3 hours, growth is slowed down, then there is progressive lysis, which becomes complete in a few hours if the quantity of penicillin is sufficient. Lysis is at its maximum when growth is most active. Lafaïlle, Sureau and Berrod⁴² have shown that the toxicity of penicillin to cultures of diphtheria bacilli is inversely proportional to the age of the culture.

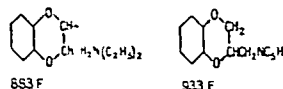
As it was not generally accepted that there is a synergy of action between penicillin and sulphonamides, this subject was reinvestigated at the Institut Pasteur both experimentally and clinically. Nitti, Boyer and Faguet read a communication⁴³ to the Association des Microbiologistes de Langue Française in January, 1946, in which they showed the undoubted value of combining these two drugs in experimental streptococcal or pneumococcal infection in mice. This synergy is logical, as the two drugs act in different ways. The experimental findings *in vivo* have been confirmed both by tests *in vitro* and by clinical experience.

These conclusions are fully supported in the excellent book by Martin and his collaborators⁴⁴, and in Simonnet's memoir⁴⁵.

Treatment of Functional Disorders

The origin of the investigations undertaken in the Laboratories of Therapeutic Chemistry on poisons of the autonomic nervous system is to be found in the partly accidental observation that adrenalin is antagonized by the aminomethylbenzodioxan derivatives Fourneau 883 and Fourneau 933 (Fig. 10), which were first synthesized in connexion with

FIG 10



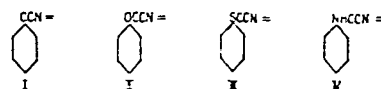
our research programme for the discovery of antimalarial drugs. In these derivatives sympathicolytic action is found at its maximum, paralysis, or reversal, of the effects of adrenalin appears after a very small dose and affects a very

great number of organs and functions: blood-pressure, capillaries, heart, iris, nictitating membrane, unstriated muscles of the intestine and uterus, bronchi and melanophores⁴⁶.

The fact that the physiological activity of the aminomethylbenzodioxans is connected with the exact correspondence of the molecule and some cellular structure stands out with particular clarity from the work which has been done on the stereo-isomers. The ratio between the pharmacodynamic activity of the left and right isomers⁴⁷ is 6:1 and in some cases 20:1.

Later we turned our attention to the problem of the mode of action of these substances and in particular to the structural relationships which would permit the comparison of adrenalin and the sympathicomimetics with their antagonists. Apart from the well-known series of the benzylethylamines (I), we discovered the sympathicomimetic activity of several series of new derivatives: the phenoxyethylamines (II), the benzylethylsulphides (III) and the benzylethylenediamines (IV)⁴⁸ (Fig. 11), each of these new series being, moreover, an

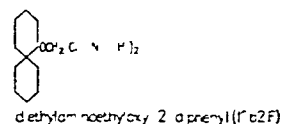
FIG 11



intermediary stage between what are usually called the sympathetic "stimulants" and their antagonists, the sympathetic "paralyzers". We have described new synthetic sympathicolytics in this way in the following chemical series: phenoxyethylamines⁴⁹, aminomethylcoumarins⁵⁰, benzylethylsulphides⁵¹, benzylethanolhydrazines⁵², aminobenzylmorpholines⁵³ and benzylethylenediamines⁵⁴.

As the result of a suggestion that we should extend the field of investigations begun by our researches on the phenol esters and the aminomethylbenzodioxans, we were led to study the antagonism shown by a whole series of new diphenyl esters to fibrillations caused by physical or chemical agents. The systematic study of these showed that the most active group of this series was diethylaminoethoxy-2-diphenyl or Fourneau 1262⁵⁵ (Fig. 12). This product is now used in the treatment of angina pectoris.

FIG 12

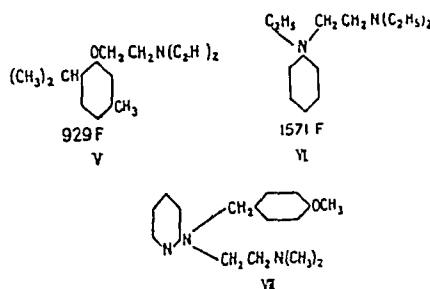


The pharmacological study which grew out of the investigation of the phenol esters also led us to the conception of antihistamine poisons. It is well known that the biologically highly active amines, acetylcholine, adrenalin and histamine, are related in their chemical structure, distribution in body fluids and pharmacodynamic properties. It thus appeared likely that, just as there are alkaloids capable of opposing the effects of acetylcholine and sympathicolytic poisons which neutralize or reverse the effects of adrenalin, there might be substances possessed of a specific antagonism to histamine. These synthetic antihistamine compounds were discovered, in our laboratory, in three chemical series derived respectively from phenol (V), aniline (VI) and aminopyridine

HISTORY

(VII) (Fig. 13) N - p - methoxybenzyl - N - dimethylaminoethylaminopyridine (VII) neutralizes the toxic effect on the guinea-pig of 100 toxic doses of histamine, and acts with a dose as low as 0.1 mg. per kg. Both in France and abroad

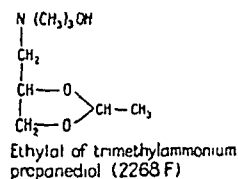
FIG. 13



extensive work has established as classic the conception of the specificity of the action of the histamine antagonists and the explanation of their action by postulating a blocking of the specific peripheral receptors. Experiments carried out with products of this type provide an additional proof of the part played by histamine in anaphylactic shock. The antiallergic action is clearly apparent in anaphylactic shock in guinea-pigs, rabbits and dogs, in the Sanarelli-Schwartzman reaction and in the Schutz-Dale phenomenon. Various products from these series are now used clinically in serum sickness, urticaria, Quincke's oedema, and various forms of asthma.^{46, 47}

A recently obtained member of the group of acetylcholine derivatives—ethylal of trimethylammonium propanediol (Fourneau 2268) (Fig. 14)—probably represents the most

FIG. 14



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- ² Nicolle, M. & Mesnil, F (1906) *Ann Inst Pasteur*, 20, 417
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- ⁴ Fourneau, E. Navarro-Martín, A., Tréfouël, J. & Tréfouël, J., Mme (1923) *Ann Inst Pasteur*, 37, 551
- ⁵ Fourneau, E., Tréfouël, J., Mme & de Lestrangé, Y., Mme (1926) *Ann Inst Pasteur*, 40, 933
- ⁶ Fourneau, E., Tréfouël, J., Mme & Benoit, G. (1927) *Bull Soc chim Fr sér 4*, 41, 499
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- ¹⁶ Marchoux, E. (1925) *Ann Inst Pasteur*, 39, 197, (1925) *C R Soc Biol Paris*, 92, 132
- ¹⁷ Fourneau, E., Tréfouël, J., Tréfouël, J., Mme, Stefanopoulou, G., Benoit, G., de Lestrangé, Y., Mme & Melville, K. I. (1930) *Ann Inst Pasteur*, 44, 503
- ¹⁸ Fourneau, E., Tréfouël, J., Tréfouël, J., Mme, Bovet, D. & Benoit, G. (1931) *Ann Inst Pasteur*, 46, 514
- ¹⁹ Fourneau, E., Tréfouël, J., Tréfouël, J., Mme, Bovet, D. & Benoit, G. (1933) *Ann Inst Pasteur*, 50, 731
- ²⁰ Marchoux, E. & Chorine (1933) *Rev colon Méd Chir*, p. 399
- ²¹ Funke, A., Bovet, D. & Montézan, G. (1945) *Ann Inst Pasteur*, 72, 264
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- ²³ Tréfouël, J., Tréfouël, J., Mme, Nitti, F. & Bovet, D. (1935) *C R Soc Biol Paris*, 120, 756
- ²⁴ Fourneau, E., Tréfouël, J., Tréfouël, J., Mme, Nitti, F. & Bovet, D. (1936) *C R Soc Biol Paris*, 122, 258
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active parasymphaticomimetic derivative known, being toxic in doses of the order of 0.001 mg per kg. A similar compound is at present being studied clinically.⁴⁸

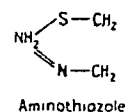
Particular mention must also be made of a new group of nitric esters of amino-alcohols, with a remarkably simple structure (Fourneau 2054) (Fig. 15) and with an action closely

FIG. 15 $\text{NH}_2\text{CH}_2\text{CH}_2\text{ONO}_2$
2054 F

allied to that of the nitrites and of trimetran, Fourneau 2054 is just as efficacious as the latter product, but is much less toxic.⁴⁹

In a series of publications we have described the experimental and clinical findings obtained with aminothiazole (Fig. 16) in counteracting thyroid function and in its use for

FIG. 16



the correction of hyperthyroidism. It may be concluded from the clinical researches carried out in France, that aminothiazole, by reason of its almost complete innocuity, appears to take pride of place over other substances previously suggested, such as thiourea and thiouracil.⁵⁰ The experimental work has been based on both pathological and physiological studies. By means of a technique which makes use of radioactive iodine, it has been possible, in tests carried out in collaboration with Joliot-Curie, to show that, in the living animal, aminothiazole antagonizes the synthesis of thyroxine.⁵¹

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- ⁵⁶ Lwoff, A., Nitti, F. & Tréfouël, J., Mme (1941) *Ann Inst Pasteur*, 67, 173
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- ⁵⁸ Nitti, F., Tabone, J. & Mousset, H. (1942) *Ann Inst Pasteur*, 68, 474
- ⁵⁹ Nitti, F. & Tabone, J. (1942) *Ann Inst Pasteur*, 68, 360
- ⁶⁰ Tabone, J. & Nitti, F. (1942) *Ann Inst Pasteur*, 68, 416
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- ⁶³ Tabone, J., Nitti, F., Senecal, M. & Mousset, H. (1943) *Ann Inst Pasteur*, 69, 253
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- ⁶⁷ Nitti, F. (1939) *Bull Acad Méd Paris*, 122, 432
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CLAUDE BERNARD AND SCIENTIFIC ADVENTURE

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The importance of Claude Bernard as one of the chief founders of modern experimental physiology was recognized even during his lifetime and his fame has grown with the passing years. A reviewer's statement that all recent French philosophy of science takes its origin in Claude Bernard¹ may be an exaggeration, but at least it testifies to the growing realization of his significance as a scientific philosopher. Within the last 10 years a number of his philosophical writings have appeared in print for the first time, and his *Principes de la médecine*, which was still unfinished at his death, now awaits publication. J M D Olmsted's detailed and scholarly biography², which appeared in 1939, is now followed by a more popular exposition of Bernard's life and work by Raymond Millet, entitled *Claude Bernard ou l'aventure scientifique*³.

It would be difficult to achieve for Bernard what Valléry-Radot so nobly accomplished for Bernard's fellow-countryman and contemporary, Louis Pasteur, and it would be almost impossible to find in Bernard's life and work the popular appeal to be derived from many writings on men such as Paul Ehrlich, yet M. Millet has almost achieved the impossible. Although Michael Foster's biography of Claude Bernard, published in 1899⁴, describes the scientific career of the great Frenchman, it makes little attempt to depict him

as a human being, and indeed the picture of his life as a whole began to emerge only with the publication of Olmsted's masterly study. The development of the portrait thus begun is well carried forward by M. Millet's latest work.

The outlines of Bernard's life are easily told. He was born in 1813 at Saint-Julien-en-Beaujolais of peasant stock. While serving as assistant to a pharmacist in Lyons at the age of 20 he wrote and had professionally produced locally a comedy sketch entitled *La Rose du Rhône*. Thus encouraged, he gave up pharmacy for the composition of a full-blooded five-act drama, *Arthur de Bretagne*, which, in 1834, at the age of 21, he took to Paris. There he was advised by M. Girardin, the critic, to study medicine rather than the drama, advice which he followed, albeit somewhat crestfallen. Qualification in medicine was quickly followed by appointment as assistant to Magendie, then professor of medicine at the College de France, whom Bernard later succeeded. His discovery that the liver secretes sugar (*Nouvelle fonction du foie*, 1850, 1853)⁵ and his isolation of glycogen (1857) quickly established his fame as an investigator of first rank.

It is no exaggeration to say that during his active years there was no field of experimental physiology which did not receive some attention from Bernard, and to almost every subject that he submitted to investigation he made some substantial contribution. But scientific fame accompanied domestic unhappiness, culminating in formal separation from his wife and daughters in 1870. His wife had from the first been unsympathetic and even antipathetic to her husband's investigations, involving as they did vivisection, and it must be confessed that in some ways Bernard was not a lovable personality. His own account of how he took a sick dog home for the week-end in order to observe closely the development of the animal's illness may well give a clue to the background of his domestic unhappiness. About the time of the legal separation from his wife, there developed an apparently platonic friendship between Bernard and

Mme Marie Raffalovich, a friendship which lasted until his death in 1878. There are still preserved in Paris some 500 unpublished manuscript letters from Bernard to Mme Raffalovich written between 1869 and 1878. The light these throw on Bernard's private life at this time is of unique importance.

To the man of science, the development of Claude Bernard's researches holds perhaps more interest than the revelation of his domestic affairs, or the assessment of his worth as a scientific philosopher. Like other classics, many of Bernard's writings are seldom read, nevertheless, their putative contents are often handed down from textbook to textbook like a precious heirloom of alleged but unascertained worth. His views on the question of whether or not liver-glycogen can act as a storage-form of administered glucose are usually mis-stated, and examination of his writings in some detail shows Bernard's own uncertainty on this point⁶. Likewise his views on the glycogenic function of the liver are sometimes much more lucidly expressed in textbooks than in Bernard's own writings.

Some of his earlier publications can give courage to those struggling with their own difficulties by demonstrating the enormity of some early mistakes of the great physiologist. There can be little doubt that the results of his investigations on secretory nerves coloured, and coloured in false tones, all his early ideas on the secretion of sugar by the liver, and his early belief that section of the vagus supplying the liver causes the disappearance of sugar from that organ⁷ arose naturally from a preconceived idea that the vagus must be the secretory nerve concerned. It was such preconceived but incorrect notions that led to the discovery of *piqûre "diabetes"*, and to the interesting theory that the stimulus to the secretion of sugar by the liver was initiated in the lungs and carried by the vagus to a nervous centre in the medulla, whence it reached the liver by way of the spinal cord and splanchnic nerves⁸.

It is clear, too, that many of Bernard's early experiments on carbohydrate metabolism were carried out under such unphysiological conditions as to yield results quite inapplicable to the normal animal. In this respect F. W. Pavy's criticisms⁹ of Bernard's early experiments were well justified. As a young English medical graduate, Pavy had visited Bernard's laboratory in 1854 and had seen repetitions of the experiment whereby Bernard had demonstrated that the liver of the starving or meat-fed dog secretes large amounts of sugar. In this experiment section of the medulla was first carried out in order to arrest life "in an essentially normal state", the blood of the hepatic veins was then demonstrated to contain an abundance of sugar while the blood of the portal veins contained none. On his return to England, Pavy decided to investigate the disappearance of the sugar from the blood when it was perfused through surviving lungs, and for this purpose he withdrew blood from the right heart of the unanaesthetized living dog by catheterization of the jugular vein. To his surprise he found that blood obtained in this way contained little or no sugar

unless the animal struggled or became asphyxiated. When, however, an animal was killed, the right heart was found to contain an abundance of sugar. As the result of these and many other experiments, Pavy concluded that Bernard's glycogenic function of the liver was a pathological phenomenon of no relevance to the living normal animal. Finding later that the sugar content of the portal-vein blood was significantly higher than that of the hepatic veins for some time after a dog had ingested a carbohydrate meal, Pavy concluded that the liver was an organ which absorbed rather than secreted sugar, converting the absorbed glucose into glycogen¹⁰. This was in direct opposition to Bernard's ideas and a controversy developed which was still unresolved at the time of Bernard's death¹¹. To the end of his long life (he died in 1911), Pavy maintained that the production of sugar by the liver was a phenomenon of pathological but not of physiological interest, despite the ever-increasing body of evidence in support of Bernard's view that the secretion of sugar by the liver was an essential factor in the economy of the normal animal.

Although his work is now largely forgotten, it is clear that many of Pavy's criticisms of Bernard's work were justified. In his early experiments, carried out on a pithed or dying animal, Bernard must have stimulated hepatic glycogenolysis to a substantial extent, so that the sugar content of the blood of the hepatic veins became quite abnormally high. In his early investigations Bernard was unable to find any sugar at all in the portal-vein blood of the starving dog, and it seems very probable that if his experimental conditions had not resulted in the stimulation of hepatic glycogenolysis, he would have missed the sugar in the blood of the hepatic veins as well as that in the blood of the portal vein, and would thus have failed to discover the glycogenic function of the liver and would not have isolated glycogen. Pavy, on the other hand, was able to detect the sugar in portal vein blood in his earliest experiments but, because his carefully chosen conditions prevented post-mortem hepatic glycogenolysis, he concluded that the blood in the hepatic veins contained the amount of sugar which was normally indistinguishable from that of the blood in portal veins.

In his experimental facts, Pavy was therefore far nearer the truth than was Bernard at that time. Hence, the curious paradox arises that, if Bernard had chosen more physiological conditions for his early experiments, he might never have discovered glycogen and the glycogenic function of the liver, while if Pavy had been a little less rigid in his determination to use strictly physiological conditions, he might not have been led to develop his incorrect theories of carbohydrate metabolism. Undoubtedly Bernard's strength lay in his ability to discard ruthlessly an incorrect theory once he was led to conclude that its experimental bases were at fault, an ability which Pavy did not share to such a marked degree. Nevertheless, the fact that Claude Bernard, a man of Olympian aloofness of intellect, could at times make such egregious mistakes, may bring some degree of comfort and consolation to us all.

¹ *Claude Bernard's triumph*. *Times Literary Supplement* 15 June 1946 p. 277.

² Olmsted J. M. D. (1939) *Claude Bernard Physiologist*. London.

³ Millet, R. (1945) *Claude Bernard ou l'aventure scientifique*. Paris.

⁴ Foster, M. (1899) *Claude Bernard*. London.

⁵ Bernard, C. (1850) *C. R. Acad. Sci. Paris*, 31, 374. (1853) *Nouvelle fonction du foie considéré comme organe producteur du matériel sucré chez l'homme et les animaux*. Paris.

⁶ Young, F. G. (1937) *Ann. Sci.* 2, 47. cf. Olmsted (1939) p. 202. Bernard, C. (1850) *C. R. Acad. Sci. Paris*, 31, 571. (1855) *Leçon -*

Physiologie expérimentale. Paris. Vol. 1, p. 324.

⁷ Bernard, C. (1853) *Leçons de Physiologie expérimentale*. Vol. 1 p. 327.

⁸ Pavy F. W. (1854-55) *Proc. roy. Soc.* 7, 371. (1860) *Philos. Trans.* 150, 49.

The Library

Publications discussed or listed in this section may be borrowed by inquirers resident in the United Kingdom on application to the Editor

936

PHYSIOLOGY OF THE HUMAN EYE

A. Magitot *Physiologie oculaire clinique* Masson Paris, 1946. 750 francs

Though ophthalmology is rich in monograph literature on the comparative physiology of the eye, there are remarkably few systematic expositions on the physiology of the human eye possibly because the subject is so fluid. The publication of *Physiologie oculaire clinique*, by A. Magitot, is therefore particularly welcome. The author has himself contributed extensively to the subject, particularly on the physiology of the intraocular fluids, and this book brings together critically and exhaustively a mass of scattered information on ocular physiology generally. The field covered is extensive, as is seen from the chapter-headings. There are fifteen sections, several of them containing subdivisions: i. Protective mechanism of the globe ii. Ocular sensitivity iii. Nutrition of the globe iv. Intraocular fluids v. Ocular tension vi. Circulation of the conjunctiva vii. Cornea viii. Iris and pupil ix. Lens x. The retina xi. The function of the retina xii. The optic nerve xiii. The visual cortex xiv. Ocular muscles and ocular motility xv. Binocular vision.

This treatise has Gallic elegance and clarity—to use an over-worked but thoroughly applicable phrase. It is extensively illustrated and the presentation leaves little to be desired. The bibliographies at the end of each chapter, whilst not exhaustive, are adequate.

The book is intended for the clinician. It lacks any discussion of the refractive state, and contains but little on physiological optics, but these subjects are adequately covered by existing monographs. Magitot's treatise is particularly good in the stress it lays on general physiology in the understanding of the physiology of the eye, and on the significance of the study of pathological states in the problems of physiology. It should do much to give ophthalmologists an insight into the basic problems of their specialty, and should greatly stimulate clear thinking. The book is likely to establish itself as a standard volume.

A. Sorsby

937

KIENBOCK'S DISEASE

Jacques Rudolf Rüttner *Beiträge zur Klinik und pathologischen Anatomie der Kienbockschen Krankheit (Lunatummalacie)* Benno Schwabe Basel 1946. 4 francs

Since Kienbock first described an unusual disease of the os lunatum characterized by softening and sclerosis, deformity, axial compression and even fragmentation, much discussion has followed about its nature. Roughly speaking, three main views have been advanced. It has been suggested that there is initial trauma, with secondary dystrophic changes in the bone leading to deformity, and certainly the frequent history of a primary fracture has given support to the view. A second theory holds that a disease of the bone is concerned, and that the other features result from this. Axhausen, for instance, has emphasized aseptic necrosis of the os lunatum due to embolism, micro-organisms of low virulence lodging in the vessels of the bone and producing a bland infarct. Others have described endarteritis obliterans or vascular spasm as the mechanism of infarction. The third view would place Kienbock's disease with the more general osteopathies such as malformations, metabolic upsets, deficiencies in vitamin and hormone supply.

In a recent study of 14 cases, Rüttner gives good reasons for regarding the pathological picture from a dynamic point of view, for the variable features depend upon intensity and duration of mechanical influences and how long the reactive process has been going on. The dominating histological change is a

disturbance of healing of a fracture. Primary callus is formed, but undergoes degeneration and softening, leading to the formation of secondary fractures and clefts. These may be complete or partial, so that only small areas of the os lunatum are affected, on the other hand, deformity may be pronounced. Pseudarthroses often form, and disturbances of cartilage and spongy bone are not uncommon. The latter include aseptic necrosis, cyst formation, medullary fibrosis, lysis and sclerosis of the true bony substance. Rüttner found no sign of primary necrosis in his cases, all of which gave clinical and roentgenological evidence of traumatic fracture in the first instance. He suggests that displacement of a fragment through the subchondral cortical ring of bone results in weakening of the spongy tissue because of lacunar resorption and softening immediately around the site of fracture, and predisposes to further fractures at a later date. In such a way are laid the foundations of a progressive pathological process, and from this comes the pseudarthrosis, atrophy of the spongy tissue with splitting, cyst formation and the rest.

With so many processes at work in the components of the os lunatum it is not surprising that a highly complicated x-ray picture is seen in the fully developed case, but a rational explanation follows from the pathological studies outlined above.

Treatment of Kienbock's disease is still far from satisfactory and Rüttner concludes that conservative therapy is better than extirpation of the bone. A follow-up of a number of his cases showed that functional disability often persisted in the joints concerned when operation was performed.

This is an excellent little monograph, full of useful information and written with a pleasing economy of words. Of the fifty odd references listed, one only is in English. Presumably a Swiss investigator can at least read that language.

G. R. Cameron

938

INFECTIOUS ANAEMIA

G. Hemmeler *L'anémie infectieuse* Benno Schwabe Bâle 1946. 5 francs

Dr G. Hemmeler has written a monograph of 76 pages on the anaemia associated with infection. He presents in some detail his own studies of the peripheral-blood and sternal-marrow pictures in a large series of cases of different types of infectious diseases, and also discusses some experimental observations on rabbits. He concludes that the anaemia is due to a toxic action on the marrow, causing hypoplasia of erythropoietic elements.

Unfortunately no post-mortem reports on the character and extent of the marrow are given. He concludes from the sternal puncture alone that there is a hypoplasia of erythropoietic elements. It is generally recognized as important to know exactly how much active marrow there is in the skeleton before attributing any form of anaemia to marrow insufficiency.

Dr Hemmeler confines his review of the literature almost entirely to continental work, and he appears unaware of important observations that have been published in England and America in this field.

His own observations offer nothing new in the way of facts, and his theories appear to be based on insufficient evidence.

939

FRENCH CLINICAL EXPERIENCE OF PENICILLIN

R. Martin F. Nitti B. Sureau & J. Berrad *La pénicilline et ses applications cliniques*. Editions Médicales Flammarion Paris, 1945

The authors of this book are all members of the staff of the Institut Pasteur and its hospital, and have been working on penicillin, at first with very scanty material and information at their disposal, since late in 1943. While, therefore, a large part of the book is inevitably based on the work of foreign writers, the authors have been able to make a considerable contribution from their own experience.

The book is divided into two parts: the first deals with the biological properties of penicillin and its preparation, while the second—by far the larger section—is purely clinical. This section is subdivided according to the type of infection to be treated. It contains chapters on infections due to staphylococci, streptococci and pneumococci, meningitis, pulmonary infections, venereal diseases, war wounds, oto-rhino-

laryngology, ophthalmology (The chapter on ophthalmology is contributed by Dubois-Poulsen, while Marc Iselin and André Aubin collaborated in those on pulmonary infections and oto-rhino-laryngology respectively) The illustrations are numerous and of a high standard and there is a bibliography of 662 references

940

GEOMEDICINE

Richard Upjohn Light *The progress of medical geography*

J K Wright *A proposed atlas of diseases, with a note on the terminology of certain map symbols*

Reprinted from *Geogr. Rev.*, 1944, 34, No 4 pp 636-654 American Geographical Society, New York

Garrison, the American medical historian, pointed out in 1932 that a new science of geomedicine was in process of being born, and Sigerist, director of the Institute of the History of Medicine at the Johns Hopkins University, has favoured the publication of an atlas showing the geographical distribution of diseases in time and space In 1944, the American Geographical Society sponsored the project for an atlas of diseases, to be designed primarily as a tool for research rather than as a popular text-book

For the proposed atlas there are two methods of approach according to circumstance the first is to attempt to narrow the selection down to the two or three best average projections, the second is to treat each disease as a separate problem and to use the projection best suited for showing that particular disease A comprehensive plate illustrates the range of symbols for use on maps, qualitative symbols for differences in kind only and quantitative symbols for differences in degree as well as in kind The inadvisability of trying to crowd too many kinds of data on one map is wisely emphasized

[The pilot project for the proposed Atlas of Diseases is reviewed below]

Anastasia van Burkalow *Fluorine in United States water supplies* Reprinted from *Geogr. Rev.* 1946, 36, No 2, pp 177-193 American Geographical Society New York

A small amount of fluorine, about 1 part per million, is necessary for optimal dental health Where the fluorine-content of the drinking water is much less than this, the dental-caries experience rates are high, where it is greater, the disfigurement known as dental fluorosis, or mottled enamel, is endemic Because of this direct relationship between dental health and an element of the physical environment, the water supply, a study of the problem was chosen as the pilot project for the American Geographical Society's proposed Atlas of Diseases, the primary purpose of which is to show the correlation of disease with the natural and social environment

The inclusion of a fluorine test is of recent development in water analysis, and incompleteness of data is therefore one of the major problems to be faced Suggestions are made as to how present knowledge can best be utilized for epidemiological study in the United States

Information on the amount and distribution of fluorine in rocks is still far from complete, but enough is known to indicate that it is present in markedly differing amount in different kinds of rocks Fluorine in soluble forms may be expected in large amounts where two conditions prevail (i) an abundance of fluorine-containing minerals, supplied either directly from magmatic sources, or indirectly by the weathering and erosion of igneous rocks, (ii) an abundance of pyrite, usually found in association with concentrations of organic material, to facilitate the decomposition of fluorine minerals The need for better data on the fluorine content of potable and agricultural waters is urged upon county and state health authorities Tests should be repeated on the same wells at different seasons The results should be considered in relation to the depth of wells, to populations using the supply (both human and animal) and, wherever possible, with rock analysis at well depths

Investigations on the lines suggested might well be considered together with the published findings of research on endemic fluorosis already carried out in Britain Comparative surveys in different countries would rapidly increase our knowledge of fluorine and its various manifestations The present communication is therefore to be welcomed It may be pointed out that

while the human bone lesions in endemic fluorotic areas of India, Argentina and South Africa are mentioned, those described in Texas in 1943 by Linsman and McMurray are not considered

941

MEDICINE AND SURGERY IN THE USSR

V P Filatov *[Optic transplantation of the cornea and tissue therapy]* [in Russian]

Professor Filatov's fundamental work on the transplantation of the cornea and the subsequent tissue therapy has opened a new era in ophthalmology This book is based on his experience of over 1,000 transplantations It is a most detailed account with excellent illustrations and diagrams The first part deals with the transplantations proper and the second with the therapeutic use of conserved tissues in the diseases of the eye, as well as in diseases which are not connected with the eye It should be of invaluable interest to all ophthalmologists

U M Oslitand *[Modern methods of electro-diagnosis in gun shot wounds of the nervous system]* [in Russian]

Diagnosis by means of electricity of injuries of the nervous system was invaluable during the war It not only confirms the diagnosis, but is also most useful for the prognosis and treatment, especially as regards the necessity of surgical interference It is mostly used for injuries of the peripheral nervous system This little book gives a compact but detailed account of all its uses The author considers that the chronaximetric method is the most perfect method of electro-diagnosis

A N Obrosova *[The technique of physiotherapy]* [in Russian]

This short manual on the technique of physiotherapy is meant for doctors and sisters of physiotherapeutic departments of hospitals It gives details of the construction of physiotherapeutic apparatus, stationary and portable It also deals with the electrical processes, which transform the electric current into different therapeutic agents There is a chapter which describes the possible defects of the apparatus and how they can be avoided by the workers using it It is a short but very useful manual for the personnel of the physiotherapeutic departments of hospitals

Yudin *[The surgical treatment of gastric and duodenal ulcer]* [in Russian]

This is based on Professor Yudin's 25 years' experience in that sphere of surgery From 1928-1943 Professor Yudin performed 5,322 operations for various conditions which are tabulated under (a) malignant growths, (b) chronic ulcers, (c) perforations, (d) haemorrhages, and (e) other causes It is a short book, but it gives a very concise account of all these conditions and the kind of operation performed It contains a number of excellent photographs of the various stages during the operations The final chapter deals with the gastric and duodenal ulcers in war-time This is a most interesting and valuable book by an acknowledged master of surgery

V N Sheiniss *[The treatment of injuries of fingers and the wrist during the war]* [in Russian]

This little pamphlet deals with the first aid, the débridement, the immobilization and the subsequent treatment of injuries of the fingers and the wrist

[The organization of scientific work in institutions of public health in the USSR] [in Russian]

This is a report of a meeting of the Scientific Medical Council, which was held in Moscow on April 18th-20th, 1945 It contains a short report of 9 eminent professors of the USSR dealing with their respective subjects, followed by an address by the Minister of Health, A F Tretiakova It gives also an account of the discussion and ends with an order by the Minister of Health on the activities of the scientific medical organizations and a resolution of the Council

H W Swann

Book Reviews

'The prices quoted are those which obtain within the United Kingdom. Editors of overseas medical journals who wish to review publications of which notices appear are invited to apply to the Editor for review copies, of which a few are sometimes available. Orders for any of the publications mentioned may be sent to the Editor if there are difficulties in obtaining them locally. Publications may be referred to by the numbers given at the left of each item, e.g. Book 942. It should be noted that supplies of all publications are limited and there can be no certainty that publications ordered or requested for review will be available. Publications are classified according to the Universal Decimal Classification and the classification number of each publication is given at the right.'

ANATOMICAL EPONYMS

942

611 (92)

Anatomical Eponyms being a Bibliographical Dictionary of those Anatomists whose Names have become incorporated into Anatomical Nomenclature, with Definitions of the Structures to which their Names have been attached and References to the Works in which they are described

Jessie Dobson LONDON BAILLIERE TINDALL & CO. 1946
x + 240 PAGES 1 PLATE, 22 x 17 cm. £1 10s. [£1 5]

Personal names are no longer recognized in official anatomical nomenclature but are still frequently used. Professor Wood Jones, in his foreword to Miss Dobson's biographical dictionary, suggests that the use of eponyms is a main incentive to learn the history of anatomy. Miss Dobson provides short summaries of the careers of eponymous anatomists and reference to the original descriptions of the parts or processes to which their names are attached. She points out that, while in biological nomenclature personal names are often given to species in honour of scientists not directly concerned with their discovery, in anatomy it is usually the discoverer whose name is recorded. Her references to original publications are thus most valuable in establishing authority for the use of eponyms, and will be of permanent use for reference, unfortunately they are not as precise as could be wished.

Her records clearly represent much research, as do her corrections of wrong attributions, for it often happens that a discovery recorded by an obscure anatomist is credited to a more famous namesake. Thus she shows that 'Bergmann's cords' have been reputedly attributed to Ernst von Bergmann, the surgeon, while they were, in fact, described five years before his birth by G. H. Bergmann, a little known neurologist.

The author has ascertained the correct dates of birth and death, etc., where variant dates have been recorded, and her facts seem generally accurate. The biographical notes are of varying value and insufficiently formalized, and little attempt has been made to indicate the relative importance of the different anatomists, for instance, there is no indication of the greatness of a Haller or a Cajal. There is uncertainty about the use of vernacular or latinized names, which could have been surmounted by fuller cross references. More careful editing and more precision in detail would have made the book considerably more worthy of the great learning which has gone into its compilation, but it is all the same an indispensable reference tool.

W R L

APPENDICITIS

943

616 345 2 002

Patients and Appendicitis

Sir Crisp English LONDON J & A CHURCHILL LTD 1946
vii + 155 PAGES 4 ILLUSTRATIONS 22 x 14 cm 10s. 6d. [£0 52s.]

(i) Patients (ii) appendicitis general aspects (iii) acute appendicitis clinical symptoms and signs (iv) treatment of acute appendicitis general principles (v) operation for acute appendicitis (vi) after treatment of acute cases (vii) non acute appendicitis (viii) indications for operation upon the non acute appendix (ix) points in technique (x) operation on the non-acute appendix (xi) modern anaesthesia (xii) the follow through. Bibliography Index

This is a little manual dealing with the many aspects of appendicitis. The author has prefaced his account by a short essay on the various types of patients with whom a surgeon has to deal, though this chapter has little direct reference to the rest of the book it is full of practical wisdom.

The rest of the book follows the accustomed lines but is of rather unequal merit. We think the detailed account of the pre-operative preparation of the patient, the enumeration of the main points of technique, and the remarks on after-treatment call attention to many valuable measures. On the other hand, the section on diagnosis is neither full nor accurate enough. The author, whose experience must have been very great, has failed to realize the difficulties of those less experienced. Otherwise why should he say on page 39, 'Diagnosis is usually obvious' and, two pages later, 'mistake is easy'. No doubt it is a misprint on page 34, which allows it to be said that the first symptom is 'often first felt between 2 P.M. and 5 P.M.', but we consider that it is quite as erroneous to state that the initial vomiting in appendicitis is often accompanied by hiccup, or to assert that 'Nausea and vomiting are often entirely absent'. Moreover, readers would have been more pleased to have the author's own account of the valuable points in differential diagnosis than an enumeration taken from a current text-book, however good.

There are certain omissions in the section on treatment. The operator who is opening an appendix-abscess is advised to let the pus out gradually and control the flow by a series of swabs; no mention is made of the invaluable help afforded by suction, which will easily keep the field dry and avoid escape of pus into the peritoneal cavity. In the description of the Ochsner treatment it is advised that nothing should be given by mouth or rectum, but no mention is made as to how the patient's fluid balance is to be maintained. Moreover, we imagine few surgeons would agree that morphine should be given four-hourly, especially since no details are given as to the dose required.

Though we agree with the author's view that repetition is often useful we think that there was no need to describe fully the various possible positions of the appendix in three different places (pages 24, 28, 95). To sum up—this is a readable account of appendicitis, not full enough in the section on diagnosis, but helpful to the practitioner who wishes guidance on pre- and post-operative treatment. It is doubtful if the experienced surgeon will find it of much value.

CHEMISTRY IN MEDICINE

944

577 1

An Introduction to Biochemistry

William Robert Fearon THIRD EDITION LONDON WILLIAM HEINEMANN (MEDICAL BOOKS) LTD 1946 x + 569 PAGES
22 x 14 cm £1 1s. [£1 0s.]

Part I Elements and Inorganic Compounds (i) The subject matter of biochemistry (ii) biological elements (iii) inorganic compounds (iv) solutions and colloidal systems Part II Organic Biochemistry (v) Classification and characteristics of organic compounds (vi) carbohydrates (vii) reactions of carbohydrates (viii) proteins (ix) amino acids and protein structure (x) lipides (xi) steroids (xii) pigments (xiii) pyrrrole derivatives (xiv) flavins (xv) melanins etc. (xvi) catalysts (xvii) nutrients (xviii) alimentary digestion (xix) intermediate metabolism (xx) carbohydrates (xxi) intermediate metabolism (xxii) intermediate metabolism (xxiii) lipides (xxiv) tissue respiration and energy exchange (xxv) purines and pyrimidines (xxvi) nitrogenous bases (xxvii) urea (xxviii) excretion (xxix) hormones (xxx) the internal environment (xxxi) blood and tissue fluids (xxxii) tissue chemistry Appendix I Food composition tables Appendix II Reagents Index.

Many text-books of biochemistry, particularly those launched more especially at the medical student, steer a somewhat unsteady course between the Scylla of chemistry and the Charybdis of physiology. Professor Fearon is, however, an expert helmsman, and the third edition of his book demonstrates clearly that the subject of biochemistry is very much more than an undigested mixture of chemistry and biology. The author of this text-book is peculiarly well fitted for the task which he has undertaken, since he is a chemist with an expert interest in analytical technique, as well as a medical man with a wide biological outlook.

The third edition of this book differs from the previous ones in the emphasis that is now placed upon certain aspects of the subject which are of particular interest in clinical medicine. Furthermore, the chapter on 'Nutrients' has been almost entirely rewritten, and a new chapter added on 'Tissue chemistry'. Since the majority of those reading this book will be medical students it is right that the author should stress subjects of especial interest in medicine but despite this con-

cession, Professor Fearon never falters in his wider treatment of the subject, a point that is perhaps of greater significance in the education of the medical student, as well as in that of the student of science, than the particular emphasis of matters of vocational importance in medicine. A typical example of his incisive, albeit somewhat forthright, treatment of the subject, based on a wide background, may be quoted from the section concerned with the biological significance of potassium in higher land-animals. "Potassium, maintaining a vegetable tradition, accumulates in the tissues, sodium, true to a marine ancestry, circulates in the fluids" (page 16).

This book conveys in a vivid fashion the unifying power which the physical sciences wield in relation to the most diverse biological phenomena. In the reviewer's opinion, therein lies much of the importance of biochemistry to the medical student. During his pre-clinical period he should not merely equip himself with the technical information required to walk the wards intelligently, this immediately utilitarian aspect of the importance of chemistry in relation to medicine is but one part of the whole. In his early years the medical student has an opportunity, which he never again acquires, to consider the principles which underlie biological phenomena in general. In biochemistry he can learn to regard biological systems—the cell of the protozoan and the tissues of the higher animal alike—not only as subjects for visual examination on macroscopic and microscopic planes, but also as objects for consideration on a sub-microscopic, molecular basis. In learning to regard living tissues in terms of molecules, atoms, ions, and the forces acting between them, the student of medicine creates a bond with his fellow in science which can illuminate his pathway, not only through his clinical studies, but also through the years of future medical advance, for it is sure that the advance of medicine in the future must depend more and more on the application to biology of the basic concepts of chemistry and physics.

The medical student who studies inorganic chemistry early in his course sometimes finds but little straightforward connexion between his early work and his later studies in biochemistry and physiology. In Professor Fearon's book he finds two chapters devoted to the biological significance of elements and of inorganic compounds, and a most interesting discussion of the position in the periodic table of elements of particular biological importance. In this and in many other ways the book shows clearly how chemistry underlies the general phenomena of biology.

The book is brilliant in conception and excellent in general accomplishment. Such excellence makes it the more necessary to consider some matters of detail which are not wholly acceptable. From the section on pages 393 and 394, concerning "Energy exchange in biological reactions", the reader may fail to distinguish between free energy and heat, and the terms "endergonic" (Coryell) and "endothermic" appear to be regarded as synonymous. Endothermic reactions can sometimes proceed spontaneously, although it is true that endergonic reactions, both in living tissues and in reactions in non-living systems, must be coupled with a course of free energy if they are to proceed to an appreciable extent.

Dogmatic statements are sometimes made about matters on which, even for the elementary student, it might be better to express some caution. For instance (page 328), "Contrary to what was once believed, sugars have no *ketolytic*, or ketone-destroying, effect, their action is anti-ketogenic in that they provide a more acceptable source of energy than the fats." Recent evidence suggests that sugars may exert a ketolytic action in providing the units of tricarboxylic acid cycle by means of which the ketone bodies may be combusted. Contrary to what is stated baldly on page 500, the pituitary growth-hormone is not lipid in character. "Oestrogenic factor" is a most confusing term to apply to pituitary follicle-stimulating hormone (page 501). The more recent evidence that nerve-degeneration in vitamin-A deficiency can result from mechanic injuries caused by pathological overgrowth of bone (Mellanby) might be mentioned with advantage on page 271. In the reviewer's opinion it is a pity that purine and pyrimidine rings are not throughout drawn in hexagon form, instead of in the old Germanic square fashion.

In spite of these minor faults, the book shows in its conception a wideness of approach to the subject which, combined with a vivid but scholarly style of writing, makes it the most readable of text-books, while at the same time, it contrives to be an important book of reference on all aspects of the subject. The general principles underlying the biochemical approach to the

problems of life have found their most able expositor in Professor Fearon, whose book may well be regarded as echoing and amplifying the works of Wordsworth.

"To every Form of being is assigned",
Thus calmly spake the venerable Sage,
"An active Principle—howe'en removed
From sense and observation, it subsists
In all things, in all natures, in the stars
Of azure heaven, the unending clouds,
In flower and tree, in every pebbly stone
That paves the brooks, the stationary rocks,
The moving waters, and the invisible air."
(The Excursion—Book Ninth)

It is to be hoped that, through the medium of this important "Introduction to biochemistry", Professor Fearon's inspired attitude to the subject will exert the widest influence on the development of biochemical thought.

F G Young

616 076

945

Micro-Analysis in Medical Biochemistry

E J King LONDON, J & A CHURCHILL, LTD, 1946 viii + 168
PAGES 16 ILLUSTRATIONS 22 x 14 cm 10s 6d [£0.525]

(i) Normal values (ii) procedures for whole blood, (iii) procedures for blood plasma, (iv) procedures for blood serum (v) procedures for cerebro-spinal fluid, (vi) procedures for faeces, (vii) procedures for urine, (viii) analysis of calculi, (ix) gastric analysis (x) hydrogen ion concentration (xi) spectroscopic procedures, (xii) tests of function, (xiii) volumetric solutions, (xiv) colorimetric and photometric measurements References Index

This new publication is an account of the current methods in use at the laboratories of the British Postgraduate Medical School, a large part of the material being a collected account of the methods developed and improved by the author and his co-workers. The book is concise and gives a complete account of the methods and of the preparation of the reagents required, but an omission in the latter respect is the preparation of Folin and Cioclteau's reagent. The applications of photometric principles are adequately presented. The author has attempted to cover the field of the common examinations of blood, urine, faeces, etc, but the amount of space allotted has apparently required the omission of such topics as the detection of sulphonamides in the urine.

The emphasis throughout the book is on the practical side, and it is to be regretted that such topics as the cleaning and calibration of glassware were not included, if necessary, to the exclusion of the brief references to clinical applications.

This book should find a welcome place on the laboratory shelf of the clinical pathologist and will also be invaluable to laboratory assistants, especially those reading for the final examination for the Associateship of Laboratory Technicians.

946

54 61

Practical Chemistry for Medical Students

William Klyne EDINBURGH E & S LIVINGSTONE LTD 1946
xvi + 460 PAGES 22 x 14 cm £1

Part I Some Fundamental Scientific Ideas (i) The nature of scientific work (ii) general ideas on qualitative work, (iii) general ideas on quantitative work Part II Practical Methods (iv) manipulation, (v) measurement Part III General and Physical Chemistry (vi) principles and their applications, (vii) volumetric analysis, (viii) experiments in physical chemistry Part IV Inorganic Chemistry (ix) reactions of common inorganic substances (x) identification of simple inorganic substances Part V Organic Chemistry (xi) principles, (xii) reactions of organic radicals (xiii) classification of simple organic compounds, (xiv) compounds of biological importance Appendices Index

This is a new book and an excellent one. Its scope is governed largely by the present medical curriculum in the University of Edinburgh, where general and inorganic chemistry, together with some physical chemistry, are studied, either in a pre-registration course within the University or in an equivalent course at school before the student is admitted to the faculty of medicine. More physical chemistry, together with organic chemistry, are then studied during the first year of the medical curriculum. In this respect the practice in the University of Edinburgh is similar to that in the majority of English medical schools. A difference exists, however, in that in Edinburgh the course in biochemistry during the second year of the medical course is taken in the department of physiology, despite the existence of an active department of biochemistry in the University. While the closest co-operation is desirable between the departments of physiology and of biochemistry (and indeed between the department of

anatomy and the other pre-clinical departments) in the teaching of medical students, the fact that there is a possibility of little or no co-ordination between the teaching of the introductory organic, physical, and organic chemistry, on the one hand and biochemistry proper on the other, is not one that will commend itself to all unreservedly.

The scope of the book is indicated by the headings of the main sections (see above).

The 23 pages devoted to fundamental ideas are most valuable and their influence runs like a streak of silver throughout the book. Too often the student of medicine studies elementary chemistry in bewilderment, missing the relationship between what he is doing in the laboratory and what he has heard in his lectures and failing to appreciate the nature of scientific thought and evidence. As Dr Klyne points out, frequent reference to the earlier chapters on scientific method will be necessary if the student is to get the most out of his laboratory work, and if he is to realize that such ideas are not confined to chemistry, but are common to all organized thought. Although it cannot be denied that the early teaching of the medical student should include tuition in the nature of evidence and the organization of thought, it is perhaps surprising that Dr Klyne's early chapters are, in a sense, an innovation in an elementary text-book of chemistry.

The section on general and physical chemistry is excellent, and the study of such general topics before the systematic study of inorganic and organic chemistry is undertaken is of great importance. There is one possible disadvantage in learning about such matters somewhat early in the course which ought to be guarded against, and that is a failure on the part of the student to recognize the general nature of the phenomena which are initially being studied in particular relationship to chemistry.

On pages 92-93 the statement is made, "Figures such as 10^{-7} or 0.000001 are clumsy to use, hydrogen-ion concentrations are therefore usually described by means of the negative logarithm of the concentration." The word "therefore" in this sentence is perhaps not the happiest of choices. It is true that figures such as 10^{-7} are clumsy in use, but surely the reason for the use of the logarithmic function is not merely convenience of notation, but because the influence on biological systems of a change in hydrogen ion concentration is determined by the ratio of the final to the initial hydrogen-ion concentration rather than by the magnitude of the increment itself. At the stage at which he first appreciates this fact, the medical student should be led to realize that a logarithmic function is of fundamental importance in biology. Even with the elementary student it could be indicated that much of his knowledge of the external world is transmitted to him by way of logarithmic functions (e.g. sight, hearing and sensory perception generally), and that the significance of logarithms in biology is certainly not limited to their use in the pH scale.

In his treatment of pK values Dr Klyne shows himself refreshingly aware of the difficulties encountered by the elementary student in this aspect of the subject. The student who meets pK values only with respect to the Henderson-Hasselbalch equation has little opportunity of appreciating the general significance of pK's, and in many instances never grasps the distinction between "dissociation constant" and "degree of dissociation." But by the use of such approximate equations as $pH = \frac{1}{2}pK_a - \frac{1}{2}\log [\text{acid}]$ and $pH = 14 - \frac{1}{2}pK_b + \frac{1}{2}\log [\text{base}]$ (both to be found in this book together with other related equations) the student himself is able to check, by means of simple measurements, the relationship between pH, pK and molecular concentration in solutions of weak monobasic acids and monoacidic bases of moderate concentration.

In the section on inorganic chemistry, the reactions of common inorganic substances are related to the periodic table in an orderly fashion, and this treatment lies at the roots of the chapter on the identification of anions and of cations (group separation). This is a first-class section, and the author is to be congratulated for the successful packing of so much useful information into a logical sequence within the scope of only 121 pages. The student who masters this section cannot possibly obtain the impression, not uncommon among elementary students even a few years ago, that the group separations employed in the identification of cations were created by a separate action of inspiration which divorced them from any other aspect of chemistry.

The section devoted to organic chemistry provides an excellent introduction to this aspect of the medical student's studies and satisfactorily relates it to what has gone before. This section

as a whole perhaps lacks some of the inspiration of the other parts of the book but it nevertheless provides an introduction to the study of more advanced biochemistry which should be most valuable. The reactions and properties of substances of biological importance are emphasized wherever their consideration is appropriate, but the mistake is not made of assuming that such matters should be introduced at the expense of the general development of the subject in its theoretical and practical aspects.

Throughout the book admirable discipline is introduced into the methods of approach to the problem in hand, the analysis of the findings and the recording of the results. The student who follows the advice of this book cannot fail to be impressed by the immense value of orderly technique.

Although Dr Klyne's book is a practical text, its emphasis of the theory underlying practice is admirable and apposite. Modern views on the nature of valency and the structure of matter are judiciously related to laboratory procedures, and with this book the student can go from theory to practice, and back again from the bench to theory, with the greatest facility. In the opinion of the reviewer this is a point of the greatest importance, and should be a subject for vigorous development in the future. Dr Klyne has made an excellent start in this direction and it is to be hoped that he will pursue this line with greater and greater force in future editions of this book.

It was Isaac Newton's inspiration that led him to write

"I am induced by many reasons to suspect that they [the phenomena of nature] may all depend upon certain forces by which the particles of bodies, by causes hitherto unknown, are either mutually impelled towards each other, and cohere in regular figures, or are repelled and recede from each other" (Preface to *Principia*).

Newton himself was unable to go far in the application of these ideas to chemical matters (see, however, Query 31 of *Optics*) and the application, to elementary ideas, of the results of modern investigations into the structure of liquids and solids, the nature of the forces binding molecules and atoms together, and of the conditions which facilitate the breaking and rearrangement of valency links, is but now beginning. It is to be hoped that within the next ten years the elementary books will all become orientated along such lines of development. Dr Klyne, with the advantage of initiating a text rather than revising an old one, has already made an exceptionally good beginning. We hope that his book will exert a widespread influence on the development of the teaching of elementary chemistry, and that he himself will be carried along by the surge he will have helped to create to cover new and hitherto unexplored ground in the new editions which, in the future, may confidently be expected.

F G Young

947

611-018 541

Physical Chemistry of Cells and Tissues

Rudolf Höber, with the collaboration of David I Hitecock, J B Bateman, David R Goddard & Wallace O Fern
LONDON: J & A. CHURCHILL, LTD 1945. xiii + 676 PAGES
24 x 16 cm. £2 2s. £2 1s.

Section I. Selected principles of physical chemistry. (i) Diffusion in liquids (ii) reaction velocity and enzyme reaction (iii) elements of thermodynamics (iv) electromotive force (v) some properties of aqueous solutions. Section II. Large molecules: their physico-chemical properties and their architectural and functional significance in living matter. (vi) interatomic and intermolecular forces (vii) some properties of large molecules in solution (viii) condensed systems of large molecules, with special reference to the structure of fibers (ix) some properties of films and membranes. Section III. Introductory remarks concerning the architecture of protoplasm. Section IV. The surface of the protoplast, its properties and its architecture. (x) the permeability of the cells to organic nonelectrolytes (xi) permeability to electrolytes (xii) permeability to weak bases and weak acids (xiii) permeability to dyestuffs (xiv) permeability to water (xv) chemistry and physics of the plasma membrane. Section V. Influence of some extracellular factors on cellular activity. (xvi) the influence of inorganic ions on cell activity (xvii) the influence of inorganic ions on fiber and cell potentials (xviii) physiological significance of the electrokinetic or ζ potentials (xix) the oil-like membranes as the seat of thermodynamic potentials (xx) the influence of nonpolar polar organic ions (xxi) the influence of ions upon cell potentials in plants (xxii) the polarization of model membranes and of natural membranes by electric current (xxiii) the influence of narcotics on cell activity. Section VI. The respiration of cells and tissues. (xxiv) The nature of respiration (xxv) energetics and kinetics (xxvi) the nature of oxidation (xxvii) respiratory enzymes (xxviii) the origin of carbon dioxide (xxix) the relation between fermentation and respiration (xxx) the utilization of liberated energy (xxxi) summary. Section VII. Contractility (xxxii) General survey of contractile tissues (xxxiii) muscles. Section VIII. Passive penetration and active transfer in animal and plant tissues. (xxxiv) Intestinal absorption (xxxv) the formation of urine (xxxvi) the permeability of the body surface of animals and plants (xxxvii) the elaboration of digestive juices (xxxviii) some remarks about the energetics of the active transfer the transferring device, and their mechanism.

It is a pleasure to read a scientific book in which the very praiseworthy aims of the authors are so admirably carried through as in this volume. The authors' aim was not to provide a text-book for the student of cellular physiology, but to present the achievements up to date, to show the trend of investigations, and to stimulate by pointing out the problems still unsolved.

For the full understanding and appreciation of the contents, considerable knowledge of physical chemistry and allied sciences is required, the authors, being aware of this, offer guidance to readers not fully conversant with physical chemistry by reference to certain standard text-books.

Starting with the presentation of some basic principles of physical chemistry, the authors proceed to problems of increasing complexity. Through the discussion of forces involved in the linkages of atoms and molecules, and of the properties and behaviour of molecules of high order or aggregation, we reach some of the most important sections in this book, those on the surveying of cellular structures, such as fibres, films and membranes. Much emphasis is laid on the properties of plasma membrane, and the authors, while presenting the various proposed models of this membrane as a mixed film, show that such a conception is inadequate. They propose to consider this membrane rather as an "active organ", through which solutes and solvent are often transferred by the performance of work against a concentration gradient between the inside and outside of the cell. It is implied that the work done by this cellular structure during such transfer is derived from the expenditure of metabolic energy. A parallel is drawn in this respect between plasma membrane and myosin fibrils, in which liberated metabolic energy is likewise utilized to perform work.

These considerations lead naturally to the chapters on cellular respiration, energetics and kinetics. It is shown how the potential energy of foodstuffs is liberated stepwise, and suggestions are offered how this energy might be utilized for cellular work.

The final sections on contractile tissues, intestinal absorption, renal secretion, permeability of the body-surface, elaboration of digestive juices are treated, broadly speaking, in the light of the previous chapters, and suggestions are offered for the interpretation of the mechanisms of active transfer at the various absorbing and secreting surfaces.

The book as a whole is of considerable importance, its authors have brought together a most impressive wealth of data and succeeded, as far as present-day knowledge permits, in giving a complete picture of cellular physiology. Apart from this, the work is a challenge to research workers for further investigations. Although the various sections were written by different authors, there is no feeling of discontinuity in passing from chapter to chapter, but one leaves the book with the conviction that it has been built on a solid framework. Physiologists, physical chemists, and biochemists will undoubtedly give a warm welcome to this work.

G P

CHILD LIFE

948

613 95 + 613 96

Child and Adolescent Life in Health and Disease: A Study in Social Paediatrics

W S Craig EDINBURGH E & S LIVINGSTONE LTD, 1946
xvi + 667 PAGES 203 ILLUSTRATIONS 22 x 14 cm £1 5s [£1 25]

Part I Historical (i) Private philanthropy [sic] and voluntary effort, (ii) voluntary hospitals and the beginnings of paediatrics, (iii) poor law care of the destitute child, (iv) welfare of school children, (v) infant and child welfare, (vi) recognition of some special needs, (vii) the adolescent. Part II Care of child life at the present time (viii) homelessness, (ix) the juvenile in need of care and protection, (x) the maintenance of health, (xi) help for the handicapped, (xii) treatment of the sick, (xiii) preparation in child and adolescent care, (xiv) the administrative background to certain services concerned with the welfare of children and adolescents (xv) the child under conditions of total war. Part III The future (xvi) The spirit of future endeavour. Part IV Legislation relating to child and adolescent welfare (xvii) Powers conferred on central and local authorities, (xviii) protection of the mother, foetal life and child life, (xix) concerning some aspects of child care under the poor law (xx) concerning educational welfare, (xxi) concerning services for the medical care of certain conditions occurring in childhood (xxii) concerning the employment of children and young persons. Appendices I Certain representative hospitals providing general medical and surgical care for children. II Certain representative special hospitals, long stay hospitals, hospital schools, residential special schools and convalescent homes for children. III Certain representative institutions, societies etc., directly or indirectly interested in the care of child and adolescent life in health and/or disease. IV Categories of handicapped pupils requiring special education. V The growth of social paediatrics. A chronological list of some outstanding events and periods. Bibliography. Index.

The title of Dr Craig's book, *Child and adolescent life in health and disease*, is very wide, but the text does really fill in

the outlines of the great subject defined by the title. In the preface he gives a concise description of the scope and aim of the book. 'The present-day picture of the provisions for the care of child life and health can be compared to an unfinished jig-saw puzzle. Each piece of the puzzle has its own historical background. It is the aim of this book to describe the puzzle in its present unfinished form, and as an aid to completion of the puzzle to explain how past progress has been achieved.'

The subject of the child and the adolescent is under active discussion at the moment, and the discussion is a political one in that there is a keen awareness that the polity of child and adolescent life is in disorder, and that its policy badly needs attention and repair. The subject is of national importance, but it is one of great complexity, and it is handled by many kinds of personnel and by many different organizations and services. The first requirement in the discussion of policy is a reliable factual account of all the agencies that attempt to meet the needs of child and adolescent life, and it is the outstanding value of the book that it supplies expert detailed information on the vast and intricate machinery, both social and medical, that ministers to all the human needs in health and in sickness of the child and adolescent. The author has had first hand experience of administration, preceded by much clinical experience, and his book is an authoritative contribution to the problem and policy of administration in the future.

Dr Craig is not content with describing the present and forecasting the future. He goes back into the history of the subject, and describes from the days of Queen Elizabeth the rise and gradual development of the many philanthropic and state agencies dealing with children. This first and historical part of the book is written with picturesque charm and accompanied by many quaint and telling illustrations. It is interesting in itself, but it is also valuable in explaining the position and form of the many pieces in the present-day puzzle picture of administration.

It would take too long to describe in more detail the different parts of this remarkable book. The sub-title describes it as a study in social paediatrics. But the word *life* in the main title is the governing word. Life in the child and adolescent has its social as well as its medical aspects, and in the book the social needs of the child in education and industry are fully described. The book is, in fact, a history, a directory, and a concordance of child and adolescent life in Britain. In writing it the author has done a great service to all who are concerned with the child and the adolescent, whether they be politicians, administrators, doctors, nurses or, last and not least, mothers. Since the publication of the book, he has been appointed to the chair of child health in the University of Leeds, and he will now have the opportunity of exercising in a great city the offices of politician, administrator, physician and teacher in the field of child and adolescent life.

A final word of praise must be given to the publishers for the number and excellent quality of the illustrations.

HAEMATOLOGY

949

616 15

Disorders of the Blood. Diagnosis, Pathology, Treatment and Technique

L E H Whitby & C J C Britton FIFTH EDITION LONDON J & A CHURCHILL, LTD 1946 665 PAGES 15 PLATES, 1 TEXT FIGURES 25 x 16 cm £1 10s [£1 5]

(i) The origin, development, functions and fate of the cells of the blood (ii) abnormal haemopoiesis and abnormal cells found in the circulation (iii) the principles and practice of haematological diagnosis I Red cells (iv) the principles and practice of haematological diagnosis II Leucocytes (v) blood platelets (vi) the principles and practice of haematological diagnosis (vii) the physical and chemical properties of the blood cells and plasma (viii) the causes of anaemia (ix) the nature and mode of action of haemopoietic substances (x) idiopathic hypochromic anaemia The Plummer-Vinson syndrome Chlorosis (xi) pernicious anaemia and tropical nutritional anaemia (xii) anaemias due to disease of the alimentary tract and its associated organs (xiii) miscellaneous dyshaemopoietic anaemias Radium and X rays (xiv) Thyroid disease, (xv) anaemia in pregnancy and the puerperium (xvi) haemolytic anaemias, (xvii) the puerperal and haemorrhagic anaemias (xviii) anaemias in infancy and childhood (xix) diseases due to aplasia or hypoplasia of the bone marrow Aplastic anaemia Agranulocytosis (xx) polycythemia erythraemia and erythrocytosis (xxi) the leukemias (leucoses) (xxii) miscellaneous disorders associated with splenomegaly (leucoses) (xxiii) diseases of lipid metabolism (xxiv) infectious diseases (xxv) haemagglutination and blood transfusion (xxvi) B12

groups (xxii) miscellaneous conditions Allergy Nephritis Coronary thrombosis Diabetes Cancer (xxiii) disorders involving the blood pigments Enterogenous cyanosis, (xxiv) technique Subject index. Index of authors

A glance through the medical literature of the past few years is sufficient to make one realize that disorders of the blood have provided one of the most popular fields for clinical investigation. It is in order to keep abreast with this considerable output that the authors have produced a fifth edition of their well-known book only four years after the fourth. While this edition conforms to the general plan of the previous ones, the recent advances have necessitated considerable revision of the chapters dealing with haemolytic anaemias, haemagglutination and blood transfusion, the anaemias of infancy and childhood, and technique. The other chapters have been brought up to date also, the whole process involving an increase of sixty-two pages of text.

The authors' plea that cell nomenclature should be standardized will find considerable support all the world over, and the relatively simple terminology used by them could well form the basis for agreement. One can criticize only their faulty alignment of the haemocytoblast with the more primitive cell called haemohistioblast by Ferrata. Coloured reproductions of blood cells, which are rapidly improving as the years go by, will greatly assist in this standardization and the four new illustrations in this book, together with the adjoining explanatory sketches, show a good way of reaching this end.

One must admit, however, that the technical reproduction of the picture the eye sees is still far from perfect, and it is to be hoped that improvement in this direction in the future will coincide with the insertion of a few more illustrations into the text which could be of real value to the reader. Important examples are the various cells of glandular fever, the different pictures obtained in marrow-smears from cases of myeloma, and the intra-corpuscular development stages of the four malarial parasites.

This book's chief value lies in its excellence as one for reference alike for physician, pathologist, practitioner and student. Much of the text could hardly be bettered, but, in the reviewer's opinion, the merit of the book would be considerably enhanced by a slight rearrangement of the subject-matter of its clinical section. It is admittedly difficult to know what and what not to include under the heading "Disorders of the Blood." Pathological changes in blood and marrow are divisible into two main groups: one in which they form the essential lesion of a disease, e.g. pernicious anaemia and the leukaemias, and the other in which the tissues are but one of the many possible affected by the disease process, e.g. carcinoma and Hodgkin's disease. The first group is rightly discussed very fully, and forms a most important section of the book. It is suggested that if all the diseases of the second group were handled in the manner of the good chapter on the infectious diseases, the book as a standard of reference would be much improved. At the moment too much space is taken up in the description (sometimes inaccurate, as in the case of porphyrinuria) of the non-haematological aspects of some of the diseases in the group, whereas the haematological details of these and other diseases are in contrast rather sketchy. By way of examples, the possible blood-changes and the appearance of the pathological cells in marrow-smears are all that need be described in the case of the lipodystrophies; it would be much more helpful to anyone seeking information about the blood-changes which occur in periarthritis nodosa to find it under the heading of this disease, rather than under a section devoted to the rarer eosinophilic leukaemia.

The technical section at the end is a welcome feature of the book and would be improved still further by the transference to it of the descriptions of technical methods included in the previous chapters, i.e. those of the Donath-Landsteiner reaction and the Paul Bunnell test. Quick's method for prothrombin-time estimation is sufficiently widely used to be given in detail here. There has been considerable experimental work recently on the relative merits of the different methods for estimation of haemoglobin, the references to which are included in this text. As this procedure is of fundamental importance to the clinical haematologist, a critical analysis of these methods would have been very helpful.

Whitby & Britton's is the outstanding British work on haematology and compares favourably with many of the American publications. While there is room for improvement, there is no question that it is of very considerable help to anybody interested in this branch of medical science. Its appeal can be

gauged by the publication this year of a Spanish edition and it would not be surprising if this venture were followed by translation into other languages as well.

MEDICAL EMERGENCIES

950

616

Medical Emergencies

Charles Newman THIRD EDITION LONDON J & A CHURCHILL, LTD 1946 ix + 117 PAGES 21 x 13 cm 10s 6d [£0 525]

(i) Poisoning (ii) coma (including sudden paralysis) (iii) convulsions (iv) circulatory failure (v) haemorrhage (vi) asphyxia (vii) the colics (viii) sudden insanity (ix) sulphonamides and penicillin (x) miscellaneous emergencies Index

Medical emergencies, as opposed to surgical emergencies, may be relatively uncommon, but when they do occur, they demand immediate treatment. In addition, they are liable to occur without any warning. This combination of factors means that the practitioner often finds it difficult to deal adequately with the emergency when it arises. As an aid to him under these circumstances this book can be thoroughly recommended. All the more usual emergencies are dealt with under the headings of poisoning, coma, convulsions, circulatory failure, haemorrhage, asphyxia, the colics, sudden insanity, sulphonamides and penicillin and miscellaneous emergencies. In preparing this new edition considerable revision has been undertaken.

Treatment even of an emergency, can seldom be standardized and Dr Newman forestalls criticism by his statement that he has merely given those that he feels to be the best and simplest "without alternatives, in order to give definite advice to those who seek it." Even so, it is impossible entirely to withhold criticism of some of his methods. For instance, in the treatment of barbiturate poisoning all that is said in favour of treatment with picrotoxin is that "it is justifiable", while in the treatment of diabetic (hyperglycaemic) coma, there is insufficient stress upon the necessity for the administration of adequate amounts of insulin. As is probably inevitable, the section on the sulphonamides and penicillin is out of date, but statements such as "the essential treatment of lobar pneumonia is the administration of sulphanilamide and penicillin" might well have been deleted in the final stages of proof-reading. The list of conditions dealt with is extensive if not exhaustive but Cheyne-Stokes respiration is a curious omission. In a book such as this an adequate index is essential, and in future editions this might be amplified, for instance, there is no reference under "coma" to diabetes or hyperglycaemia. For a book which may well have a considerable circulation outside Great Britain it is disturbing to find the officially discarded drachm still used, while when dosage is given in the imperial system no equivalent in the metric system is provided.

On the whole, however, this is a useful practical book which the practitioner will find most helpful in dealing with medical emergencies.

NOSOGRAPHY

951

616

Rare Diseases and some Debatable Subjects

F. Parkes Weber LONDON STAPLES PRESS LTD 1946 174 PAGES 18 ILLUSTRATIONS 22 x 14 cm 15s [£0 75]

Dr Parkes Weber believes that further progress in medical knowledge will largely be due to the study of rare diseases and syndromes. Probably many doctors share his opinion if one judges from the number of publications of rare and unusual cases in the periodicals. The author's name is closely associated with several of the rare diseases either by first important contributions towards identifying a disease (e.g. the Sturge-Kalischer or Sturge-Weber disease) or by furthering the understanding of an already established syndrome (e.g. various forms of calcinosis etc). In this small volume divided into 31 chapters, cases of a variety of rare syndromes and diseases, thoughts and opinions on debated medical subjects are presented all of which have been published at one time or another in journals. The book does not present a systematic study, but might almost be called collected papers. The chapters are devoted mostly to clinical details of the author's own patients and it is regrettable that pathological findings which might

have made for a better understanding of many cases, are available in relatively few instances. The reader will find also the description of some curiosities, e.g. how the natives of New Guinea produce "experimentally" the "boar's tusk ring money". Freudian psychology and the problem of euthanasia are admittedly debatable subjects, but one wonders a little how epigrams on fire-bombs, which were "smothered with sand" by either doctors or porters, found their way into a book on rare diseases.

G P

NUTRITION

952

612 392 01

The Vitamins in Medicine

Franklin Bicknell & Frederick Prescott SECOND EDITION
LONDON WILLIAM HEINEMANN (MEDICAL BOOKS) LTD 1946
xii + 916 PAGES, 208 ILLUSTRATIONS 24 x 16 cm £2 10s [£2 5]

(i) Vitamin A (the antixerophthalmic or anti infective vitamin, axeroptol), (ii) the vitamin B complex, (iii) vitamin B₁ (aneurin, thiamin), (iv) riboflavin (lactoflavin), (v) nicotinic acid (niacin), (vi) vitamin C (ascorbic acid), (vii) vitamin D (the antirachitic or calcifying vitamin), (viii) vitamin E (the antisterility or antidystrophic vitamin, alpha beta or gamma tocopherol), (ix) the unsaturated fatty acids and minor fat soluble vitamins, (x) vitamin K, (xi) vitamin P Index

The second edition of this invaluable book, published some four years after the first, is a tribute alike to the authors, to the publishers, and to the vitamins. The rapidity with which knowledge is growing has necessitated an increase in size from 650 to 900 pages, and opportunity has been taken at the same time to increase the number of figures from 120 to 208. There has been extensive revision of many chapters and tables and a new chapter on the essential unsaturated fatty acids and minor fat-soluble vitamins has been added.

The book contains far more than its title indicates. The chapter for each of the vitamins, which are dealt with in alphabetical order, begins with a brief historical account of the history of the vitamin up to its isolation, identification and synthesis. This is followed by a discussion of the chemical properties, methods of estimation and its distribution in foodstuffs. The food-tables which complete this part are each compiled from a number of original sources and represent the best information available. The next section deals in detail, and in most cases admirably, with the biochemistry and physiology of the vitamin—the section for ascorbic acid, for example, contains some 40 pages—and is followed by a discussion of human requirements and the many factors which modify them. The later part of each chapter deals with the specific deficiency disorder, and associated conditions, with laboratory tests for detecting deficiencies, with treatment, and finally with the often unduly and unjustifiably large number of conditions in which treatment with a specific vitamin has been claimed to be successful.

While wondering at the immense amount of work that has gone into the production of this book—it contains 4,500 references—one cannot pretend that all the original papers referred to have been dealt with very critically or that the authors have been uniformly successful in their presentation of material. With the sections devoted to the vitamin-deficiency disorders there can be no fault to find, and the photographs illustrating them are not only among the best we have seen, but are beautifully reproduced. On the other hand, for example, the discussion of the part played by thiamin, riboflavin and nicotinic acid in the enzyme systems of which they form essential parts is in several respects misleading. The evidence upon which adenylic acid is included as a vitamin is somewhat tenuous even for the pigeon, and there are one or two papers to which reference might have been made in the section on ascorbic acid. A personal criticism is the continued use of vitamin B₁ for thiamin and of vitamin C for ascorbic acid.

It is, however, ungenerous to look for small faults in what is undoubtedly the best and most comprehensive account of the vitamins in their relation to medicine in the English language. Anyone who has a copy of this book will find himself, like the reviewer, referring to it more and more. He will also find—like the reviewer—that the information he seeks, together with references to several original papers bearing upon the point, will be easy to find in Bicknell & Prescott.

RADIOTHERAPY OF CANCER

953

616-006 46

The X-Ray Treatment of Accessible Cancer

D Waldron Smithers LONDON, EDWARD ARNOLD & CO, 1946
147 PAGES, 102 ILLUSTRATIONS 27 x 19 cm £2

(i) General principles of treatment of accessible cancer, (ii) apparatus, (iii) classification of accessible cancer, staging, records and assessment of results, (iv) dosage and the biological response of tumours to irradiation, (v) cancer of the skin, (vi) cancer of the lip, nose, ear, eyelids and cornea, (vii) cancer of the external genitalia, (viii) cancer of the mouth, (ix) cancer of the cervix uteri, (x) the x-ray treatment of cancer made accessible by surgical exposure, (xi) the treatment of lymphnode metastases Appendix Bibliography Index

Radiotherapy is still regarded by many in medical practice as the "enfant terrible" of modern medicine, and not without some justification. In the control of unsuitable guardians thus relatively young branch of medicine has made, and continues to make, serious mistakes. In the hands of the trained radiotherapist, however, with a growing insight into the rationale of biological action, the infant is being tamed and can be depended upon to do his work, and not to commit the apparently capricious indiscretions which were frequent in his early days. These trends are emphasized in Dr Smithers' book, which is an attempt to show the success which can be achieved using modern apparatus, up-to-date physical knowledge, and recently developed methods of cytological investigation in association with perfected and ingenious technical methods.

The beautiful illustrations show clearly the type of case treated, and the descriptions of physical factors involved are clear and concise, but lacking in one important particular, viz. the number of treatments given. This is an omission which should be rectified in view of the importance likely to attach to this factor in fractional x-ray treatment (See Gray, L. H. (1944), *Brit J Radiol* 17, 327). The description of the x-ray apparatus and applicators used is clear, concise and well illustrated, and the isodose curves produced by Mayneord and his colleagues are clearly shown, with interesting combinations of the fields of the short-distance x-ray beams. Similar combinations are not shown for other types of x-ray beam, although the use of the 200 kV beam in the treatment of mouth cancer from outside could be usefully illustrated in such a book. The elegant devices for ensuring precision in treatment (the lens filter, moulds for positioning, and protection devices) deserve special mention, as does the emphasis placed on suitable records and their statistical treatment. The cytological investigations referred to are of two types: the differential cell-counts by the Spear and Glucksmann school, and the chromosome break investigations of Koller. Their use is not clearly emphasized, however, and one differential count (Fig 39), which is obviously unfavourable, and yet seemed to be associated with a favourable clinical response, requires some modification of the general theory to produce the truth of the matter.

A short account of the action of radiation on malignant cells puts very clearly the salient points of recent discoveries by Lea and Catchside, Mitchell, Casperson and Santesson, and Koller, which should be very useful to those unacquainted with this work. It is refreshing to find a statistical test of results in a book of this nature, but it would be sounder to compare the figures of fractionated- with single-treatment results of skin cancer in the same rather than in different clinics. The results would still show a significant difference, although the advantage of fractionation is not proved without trials of other doses in the single-treatment method.

The chapter on mouth cancer deals with a most difficult and important region too briefly, and the arguments against adequate prophylactic treatment of lymph nodes are not consistent with the view later expressed that "when the primary growth is being treated by external radiation, fields should be arranged to include likely sites of lymph node involvement". However, it has been said that consistency is the refuge of small minds.

The book is a monograph rather than a text-book, and the author is to be congratulated on a clearly and concisely written, well-illustrated presentation of the subject, although within a limited framework, based on his own experience, backed by sound knowledge and insight into the difficult subject of which he writes. The publishers and printers also merit commendation for the paper, type, illustrations and general format, which add to the pleasure experienced in its reading.

F Ellis

Films

The Scientific Film Association and the Royal Society of Medicine have been co-operating in the preparation of a reference catalogue of all the films of medical interest in Great Britain. Dr Stanford, who was in charge of this work, gives below a brief account of how it was done

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MAKING A CATALOGUE OF MEDICAL FILMS

BRIAN STANFORD, M R C S , D M R , F R P S

Until now a teacher of medicine in Britain wishing to use film has been unable to do so for lack of a unified catalogue listing the films available and suitable for his purpose. A few collections have been listed by title, but the vast majority of films lie unused because their existence is unknown. The difficulty of obtaining suitable films has led many teachers to make their own, with various degrees of success, but when an insistent request has come forward to make a film from university funds, the decision to undertake production has often been impeded because of the possibility that a film on the subject might already exist. A vicious circle thus exists by which films are either not made, or not used if made, and a reference catalogue is seen to be essential to progress.

This state of affairs was so well recognized by the Medical Committee of the Scientific Film Association (SFA) that their first action after formation in 1943 was to publish an appeal in the journals for information on the location of films of medical interest. Replies were collected and filed, but real cataloguing was held up for lack of adequate funds. A few months later it became known that the Royal Society of Medicine (RSM) was contemplating founding a library of medical films, and they too needed a catalogue to provide an estimate of the work likely to be involved. It was quickly evident that co-operation was both feasible and desired, and in January 1945 a nominee of the SFA, working on SFA procedure and financed by the RSM, started work. By March 1946 most of the films known to exist in Britain had been viewed and synopsised, and the material so collected is now being prepared for publication by the Association of Special Libraries and Information Bureaux (ASLIB). This catalogue will not, however, contain any description of the cataloguing-procedure, for a separate publication describing this is under consideration, but in the meanwhile the condensed description which follows may prove useful to other countries contemplating the preparation of a similar catalogue.

Data to be Collected

A mere list of titles obtained from written replies to a circular is not satisfactory. In the first place, the title so given is, in about 40% of the cases, not the same as the title on the film, which leads to much confusion, and secondly the title alone gives no indication of the content of the film. For example "Hypertrophic pyloric stenosis" may be a record of visible gastric peristalsis in an infant, or a demonstration of the method of administering Eumydrin, or a record of an operation for the condition, and so on. Also a written synopsis of the content of the film is desirable, because the film, unlike a book, cannot be flicked through and

an impression of its usefulness gained at a short glance.

Yet even this synopsis is not sufficient, an objective summary of what the film shows can give no indication of whether it shows it clearly or badly, whether the demonstrator's hand obscures vital sequences, whether the camera is too far away to show plainly the features it is recording, whether the facts are correct but their sequence of presentation confusing, and so on. So a written criticism of the teaching value of the film, prepared by a panel competent to pass judgment, is essential to a complete film catalogue, this is the "Appraisal". The catalogue will also list the length of the film, its gauge, whether sound or silent, colour or monochrome, copy or original, and where it can be obtained. With all this information to be obtained of necessity for each film, it is reasonable at the same time to record the authority who made the film, the photographer, and similar details (the "credits"), and it is valuable to note the methods and techniques employed in making the film.

All this information is useful to the teacher who is seeking to select the film most appropriate to his needs from the catalogue listing perhaps four or five titles which might be suitable. If he is enabled to narrow his choice to only two, he has saved much time, and the film library can reduce needless circulation of films which have by nature a limited projectable life. Cataloguing scientific films is therefore a big undertaking if performed properly, but once done the work stands for all time, and is added to as new films appear.

Staff and Equipment

It was thought essential that the viewing of each film be done by a medical man, for only he can interpret the significance of the actions portrayed, or use the correct technical terms in writing the summary. This medically-qualified viewer was employed full-time on the project. In order to make the most intensive use of his specialized knowledge, it was found necessary to give him as assistants a secretary-stenographer, a copy-typist, and a general assistant who was trained to operate the projector, to inspect, repair, pack and despatch films, and to act as messenger and filing-clerk. A 16 mm silent projector was placed at his sole disposal, and a sound machine was available when necessary. The silent machine was fitted with variable speed control (most of the viewing, even of silent films, was done at 24 frames/sec), and reverse-and-stop-mechanisms, the latter especially being needed for noting title, technical adviser, and other credits. The sound machine was not used routinely for silent films, firstly because many films were in bad condition and would not project satisfactorily on a machine having only one line of sprockets, and secondly because the lamp was overheated if the machine was used at 16 frames/sec for long intervals.

Viewing

Viewing was mostly done in a small room, on a screen 12 x 16 inches [30 x 40 cm], with a low level of general room-illumination. In this way an extremely bright image was viewed from a few feet away, with enough local light to take notes while the film was running. This was essential, for a synopsis written from memory after the film has finished is not satisfactory. With a little practice it becomes easy to look down at the note pad on one's knees and to write while the film is in progress without missing essential steps. Stopping the film for each note to be written would be tedious. To these rough manuscript notes were added a

comment on the quality and value of the film, and an arbitrary grading of merit 1—excellent, 2—useful, 3—possibly usable, and 4—useless

This grading and comment was used later in compiling programmes for the Appraisal Panels, these were presented with one film from each group—1, 2 and 3—so procuring balanced opinions, the films in group 4 were to be left until the main work was covered. The personal opinion and grading were made for the use of the cataloguer only and were never intended for publication in any form, but the value of these comments became evident later when the work on the catalogue became known, and frequent requests for assistance in programme-compilation were received. Here the cataloguer's comments, unauthoritative though they were, were found to be of great value, a point which emphasizes the need for authoritative appraisals in film catalogues

Compiling the Records

The manuscript notes were transferred in typescript to the back of a standard form, which was then filed alphabetically. In addition, other cross-references were compiled, the film-titles were listed in numerical order, and were listed under subject headings (for instance, a film on congenital torticollis would be entered under Obstetrics, Paediatrics, and Orthopaedics), the medical man responsible for making the film was allocated a filing card and the title was put under his name. As other films with which he was connected came for viewing, the titles were added to this card.

In addition to these obvious indexes, two others were found essential—a small card, 3 × 4 inches, on which was recorded the title of the film, and the stage of cataloguing that it had reached (i.e. existence known, but not traced, called for view, held for view, returned after viewing, and so on), these were filed in alphabetical order and under no circumstances allowed out of the filing cabinet. The other was a card 6 × 9 inches, on which was recorded the title, odd notes about the film, where we had learnt of its existence (e.g. by word-of-mouth from Dr —, from a review in a journal, etc.), and the dates on which it was sent for, viewed, returned to the owner, etc. This card was filed according to the stage the film had reached in our cataloguing-procedure, so that we could see at a glance how many films had been sent for, how many held for viewing, how many known of but not yet sent for, and so on. In this way a smooth flow of films was

maintained, to the back of these cards were stuck any reviews found published, or references to those reviews

Tracing and Handling the Films

The last-mentioned index card was made out as soon as we learnt of the existence of a film, whether by chance remark from a colleague, in a letter accompanying some other film, or from a published reference. The source of information, as has already been mentioned, was added. In this way news of the existence of a film was recorded instantly, and the film itself could be traced at leisure. The title was entered in pencil, for the title first heard was rarely the same as that on the film when it arrived. This true title was typed on, and if the first-mentioned title was known to be widely used it was also filed on a separate card as a cross-reference to the true title. This was often found necessary, for a film would be listed in two different catalogues with slightly different titles, and it became important to recognize whether they referred to two different films or were only variants of the same title.

The owner of the film was sent a form on which the purpose of the cataloguing was explained, and on which he was asked to give a few details about the film and to say whether he would be willing to lend it for viewing. In practice this permission was not once refused, but it was important to remember at all times that the films were private property and lent as an act of courtesy, the voluntary nature of the scheme underlay all our actions. The film was eventually sent for, and on arrival inspected, cleaned, and where necessary spliced before viewing. We aimed, wherever possible, to return the film in better condition than it arrived, this was usually not difficult, for they often came in a neglected condition. After viewing, they were rewound and returned by registered post, and a covering letter was sent separately thanking the owner for the loan.

In this way some 1,200 titles were recorded in fifteen months, and 800 films were viewed and synopsisized. Appraisal was started according to the system evolved by the Scientific Film Association, but only one subject-group, 26 films on anaesthesia, was covered before the main work of cataloguing was completed, and the information so far gathered prepared for publication. Appraisal is being continued by the Scientific Film Association, who have undertaken the responsibility of keeping the catalogue up-to-date.

Films

MORE FILMS FROM THE INSTITUT PASTEUR, PARIS

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M. Pierre de Fonbrune, who showed last January, under the auspices of the British Council, some of the cinemicrographic films made by M. Comandon and himself at the Institut Pasteur in Paris, gave two further demonstrations at the British Council Film Theatre on Monday, 15 July. Four of the films were reviewed in an earlier number of the Bulletin (*BMB* 812). Reviews of three more are given here. Applications for the loan of any of these films should be made to Cinematographic Attache, French Embassy, London.

1 CARYOCINESE

The film is chiefly devoted to karyokinesis in the mother cells producing erythrocytes in the Triton. Abundant feeding after several months of starvation produces active growth in the haemopoietic as well as other tissues, making easier the task of catching the cells when they divide. By light compression the cells are immobilized, and chromosomes, mitochondria and the rotation of the nucleus before division are demonstrated.

The movement is speeded up, and it is of considerable interest to notice lively movement of leucocytes dancing across the field. Nuclear division in a small amoeba, *acanthamoeba*, is also shown.

This film probably represents the best possible results to be obtained by these methods of photography, and it conveys, as only the film can, a vivid over-all impression for the student of this fundamental event of life, and for the research biologist details of the event, otherwise difficult to record, for close study at leisure.

2 AMOEBA VERRUCOSA

The amoeba is seen engulfing long particles of alga. The alga is seized and actively pulled into the amoeba—which answers an old problem as to whether the food of the amoeba penetrated into it by passive physical means. The long piece of alga is engulfed and coiled up in the amoeba, but this coiled-up strip is under tension and sometimes it comes undone and bursts the amoeba open. The damage is, however, rapidly repaired, and the amoeba soon starts eating again.

3 PHAGOCYTOSE

This film shows speeded up photography of blood. Attention is given chiefly to the polymorphs. Then amoeboid movements are shown, and by a lower-power view their active travelling about is demonstrated. By the use of a special micropipette, two sorts of bacteria are introduced, and the leucocytes gather round and dispose of them.

A closer analysis of the differential phagocytosis of different organisms would be possible by this method and would be of considerable interest.

The monocyte is not demonstrated, but some lymphocytes come casually into the field, and they show mobility and active contractile movements of the nucleus. These are important demonstrations for it has been considered that the lymphocyte is immobile, and that the lobulated lymphocytes seen in lymphatic leukaemia are essentially abnormal forms.

The film would be of considerable value for teaching and it is to be hoped that the Institut Pasteur will make it (and the other films) available to UNESCO for circulation throughout the world.

Ronald MacKeith

★

HEALTH EDUCATION FILMS

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Your Children's Ears

made by Realist Film Unit, 1945, owned and produced by the Central Office of Information for the Ministry of Health, in co-operation with the Central Council for Health Education, 16 mm sound, 540 ft (160 m), 35 mm sound, 1,340 ft (400 m), black and white, 15 minutes

This is one of a series of health films designed mainly to instil into parents the need for obtaining medical advice about certain childish ailments or infirmities at an early stage.

The film shows, by means of diagrams the mechanism of hearing and how this can be interfered with by neglect of what appear to be comparatively trivial matters. The diagrams are clear and explain in a straightforward simple manner how the complicated ear works.

The films would not only be suitable for showing to audiences at Maternity and Child Welfare Clinics and Women's Institutes, but might with some advantage be shown to medical students when they are working on this subject.

The principal message, that one should seek medical advice for all ailments of the ear or the throat, is well emphasized and the film should be a popular addition to any health demonstration.

Amulree

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Your Children's Eyes

made by Realist Film Unit, 1945, owned and produced by the Central Office of Information for the Ministry of Health, in co-operation with the Central Council for Health Education, 16 mm sound, 690 ft (210 m), 35 mm sound, 1,710 ft (510 m), black and white, 19 minutes

This film opens with a number of shots showing how children with indifferent sight are handicapped at school and in their normal life. It emphasizes the need for parents to seek medical advice for their children if they are in any doubt whether they can see properly. A number of shots are given showing the good effect of glasses on defective eyes. The film also explains, by a series of simple diagrams, the mechanics of the common squint, and conveys this information in a way which, although simple, could be usefully employed in the training of medical students and others interested in ophthalmics. The proper correction of this defect by means of appropriate lenses is explained simply by means of diagrams. The commentary is well done and the photography is, generally speaking, good.

This film should serve a valuable purpose in explaining in simple terms the structure, function and common defects of eyes and should encourage mothers to take their children promptly to hospital if they suspect their vision is not perfect.

Amulree

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Your Children's Teeth

made by Realist Film Unit, 1945, owned and produced by the Central Office of Information for the Ministry of Health, in co-operation with the Central Council for Health Education, 16 mm sound, 500 ft (150 m), 35 mm sound, 1,260 ft (380 m), black and white, 14 minutes

The importance of early regular and frequent visits to the dentist is the main message of this film.

The eruption of the milk and permanent teeth is shown by means of diagrams and the process by which decay is set up is well shown by means of animated cartoons. Practical instruction on the proper way to brush the teeth is given and the film could usefully be shown to any audience of parents or children.

The method of cleaning the teeth by a rotary movement always seems to make that operation rather more difficult than it need be, and it seems a pity to exclude the more straightforward ways of handling the toothbrush.

The photography is good and the diagrams are clear.

Amulree

★ ★ ★

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The Microscope

made and owned by Realist Film Unit, 1945, 16 mm sound, 410 ft (120 m), 35 mm sound, 1,040 ft (310 m), black and white, 11 minutes

The compound microscope is used extensively by pupils in senior schools and universities, yet it is exceptional for them to be given clear instruction in its use when first they meet it. This film provides much of that necessary introduction. It is divided into three parts spaced by blank film so that the teacher may stop at each stage to answer questions and teaching notes and a wall chart (which appears in the film) are provided as an integral part of the visual unit. The first part of the film demonstrates the mechanical and optical components (nosepiece, drawtube, stage, condenser, objective, eyepiece) and the lighting unit (lamphouse, bulb, iris, filter-holder). The second part shows how to set up the microscope for observation, and advocates a definite routine by which the object is first focussed while illuminated by simple transmitted light, and then the plane of the illuminator iris is focussed by the sub-stage condenser into the plane of the object. The stages of the manipulation needed are clearly shown and the proper use of sub-stage and lamp-source irises. Part three is devoted to the adjustment of the high-power objective. Here the value of accurate focussing of the sub-stage condenser advocated in part two is reinforced, for the focussing is done on the aerial image of the illuminant instead of on the



FIG 1 FOCUSING THE CONDENSER

When the pencil image is in sharp focus the image of the lamphouse opening is in the plane of the slide. This gives maximum illumination.

FIG 2 HIGH POWER FOCUSING

The image of a pencil moved in front of the light source is easy to locate even with objectives of very small depth of focus. When it is brought into sharp focus the image of the specimen flashes into view.



object, this is easily achieved by moving a pencil-point in the plane of the illuminator iris. Once this is picked up the real object will be seen, and only minor adjustment of the fine focus is needed. In this way damage to the slide (and the objective) by accidental rapid passage through the plane of focus is avoided.

This is an essentially elementary introduction—dark-ground and oil-immersion techniques are not mentioned—which will be widely welcomed in all biology training centres, for the information is clearly and accurately presented. But it may be regretted that the construction of an objective is demonstrated by taking one to pieces, for this is a manoeuvre that should not be encouraged, and a lens shown in section would have done just as well, while a demonstration of the amazing precision of the fine-focus adjustment mechanism could well have been included.

Brian Stanford

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It began on the Clyde

made by Greenpark Production, 1945, owned by the Central Office of Information for the Department of Health for Scotland, 16 mm sound, 540 ft. (160 m), 35 mm sound, 1,350 ft. (400 m), black and white, 15 minutes

At the outbreak of war in 1939 the hospital services of Britain were completely reorganized and large numbers of new hospitals established outside the cities to treat the expected war casualties from both civilian and military sources, fortunately these facilities were not immediately needed, but much skilled staff was kept idle as a result. By 1941 black-out conditions were beginning to be reflected in an increased incidence of minor disorders among factory workers, and the depleted civilian

medical service was unable to devote the time required for reassuring each of these patients. Glasgow decided that as an experiment a few such patients should be admitted at their doctor's request into the almost empty Emergency Medical Service (E.M.S.) hospitals, at least until such time as direct war casualties arrived in greater numbers. This film shows how the scheme was conceived and worked, and follows the treatment of one patient admitted to an E.M.S. hospital. Here he is investigated to see whether his apparently nervous symptoms have any organic basis, he is given appropriate physiotherapy, good food and plenty of rest in country surroundings. Under this régime his symptoms subside and he returns to work. This pilot scheme worked so well that later it was extended to include surgical cases from the hospital waiting-lists in addition to these problem patients referred by local doctors. This step also proved its worth, and the Department of Health for Scotland then applied the Clyde Basin Scheme, as this pilot system had come to be called, to the whole E.M.S. of Scotland. The film ends with a plea that although this method of treating town patients in country surroundings was successfully started under the stress of war, reversion to peace-time conditions must not allow the system to lapse.

To some extent this film fails to carry conviction, partly because we cannot remember that conditions were as bad in 1941 as depicted here, and partly because the leading actor is miscast. But the film, which has been used as one of the films of the month by the Ministry of Information, should be widely appreciated in these mechanistic times for the strong case it puts that comfort, attractive food, and pleasant surroundings are just as important as drugs and surgery in helping to cure a sick man.

Brian Stanford

Corrigendum

Vol 4 No 3

BMB 876, The genetics of cancer, by Georgiana M Bonser P 207, col 1, l 41 F_2 should read " F_1 "

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Chemical Carcinogenesis

THE present number of the *British Medical Bulletin* comes at the end of a brilliant chapter in chemical carcinogenesis, and at the opening of a new era of investigation which promises to be more intense and productive than any which have gone before. Its intention is not merely to provide a conspectus of our present knowledge, but to indicate also the probable trends of development for the years ahead.

We should like to make special acknowledgment of our indebtedness to Professor Alexander Haddow for his invaluable advice in the planning of this number. Not only has he made a substantial contribution to its matter, but it was with his advice that its general plan was devised. Other contributors, especially Dr I. Berenblum, have also offered useful suggestions, which have been incorporated.

In few modern subjects is there a stronger sense of historical continuity with the past, but we cannot too often be reminded how our present wealth of information sprang directly from the curiosity and accurate descriptive powers of the great clinical observers of the 18th and 19th centuries. In this subject, although he would be surprised to learn it, Percivall Pott must here be reckoned *facile princeps*, and that not merely in time alone. That such methods are still not only useful but indeed essential is amply shown by the articles which follow on cutaneous cancer in industry, on occupational cancer of the bladder, and on the rôle of arsenic in carcinogenesis.

Before the war of 1914-18, the workers of the Imperial Cancer Research Fund had laid the basis of what may be called the natural history of cancer: that is, the frequency and distribution of the disease in man and animals, the circumstances in which it arises, and the way in which the behaviour of cancer cells differs from that of the normal cells from which they are derived. From 1915, when Yamagiwa was the first to produce cancer under experimental conditions and at will, by application of coal-tar to the skin, investigation naturally shifted to the chemical identification of the substance responsible. It is in this field more than any other that the greatest strides have been made in the past generation, in large measure as a direct outcome of the contributions of Kennaway and his co-workers at the Royal Cancer Hospital in London.

With characteristic modesty, Kennaway has never failed to point out the influence of chance and good fortune on the course of these researches—for example, that “any further advance would have been difficult indeed if one at any rate of the carcinogenic substances in tar, namely, 3-4-benzpyrene, had not possessed the extraordinary property of blotting out with its own fluorescence that of other intensely fluorescent compounds, such as anthracene, in the complex mixture”. Although the history of cancer research provides many similar instances of fortunate circumstance, they have seldom favoured any but minds already prepared. Much more has been due to a relentless and unwearied patience (a quality peculiarly necessary in problems such as these), to systematic and well-planned experiment, and to occasional brilliant examples of the use of the scientific imagination, as in Cook's successful prediction of the high carcinogenic potency of methylcholanthrene, before that compound had actually been made. There is, of course, as we know, no lack of problems still, but the fact that there is any prospect at all of continuing progress in the future is to a large extent due to the contributions of Kennaway and his school. They represent nothing short of a new chapter, and a long one, in experimental and chemical pathology, and are a source of legitimate pride in the lustre they have added to British medicine and science.

Few of the earlier workers in this field can have foreseen its surprising growth and ramification, and especially the remarkable clues which these discoveries provide towards solving the problem of the “spontaneous” origin of cancer in man. The isolation of carcinogenic substances from human tissues is a subject which is being watched with special interest, in the belief, or hope, that from such work may come the long-awaited explanation.

With another natural and inevitable change of emphasis, interest is now tending to centre less on the description of carcinogens as such, and more on the means by which they transform the normal cell into a malignant one. Here the purely chemical attack seeks to reveal the significance of relationships between constitution and biological action, the biochemical approach concerns itself with both the intermediate and the ultimate fate of carcinogens in bodily metabolism, and the biological method considers the mutual summation and interference of different agents in carcinogenesis, and the influence of carcinogens upon normal growth. Much of the progress which has been achieved in these various directions in the past decade is summarized in those papers which deal with cocarcinogenesis, anticarcinogenesis, the influence of solvents on activity, the

metabolism of carcinogens, and the mechanism of tumour-production generally.

From these and other articles it is clear that much progress has been made, and continues to be made, towards a clearer understanding of the changes involved, and of the way in which not only chemical substances, but physical carcinogens equally, operate to bring these about. The very multiplicity of carcinogenic agents has always presented something of a problem, as to the mechanism by which agents as diverse as x rays and gamma rays, ultraviolet rays, and the chemical carcinogens, could produce an identical end-result in the shape of a malignant tumour. It now appears not only that they have in common the property of damaging or inhibiting the processes of normal growth in a rather special way, but that they should all be regarded as sources or carriers of energy in a form which readily interferes with the normal economy of the cell, and eventually leads to an entirely new orientation of characters at a different energy-level.

We therefore seem to be coming within sight of a quantitative understanding of cell-variation as a problem in energetics. If much remains to be done, there can be no doubt of the implications that such an achievement would hold, not simply for the cancer question, but for biology as a whole. From other facts, which are briefly mentioned in an article on the mode of action of carcinogens, an attractive hypothesis has emerged according to which normal growth may be regulated by the supply of specific growth-factors which individual tissues are unable to synthesize, the autonomy of the cancer cell possibly being due to an acquired power to elaborate such substances and so become independent of their external supply.

One specially noteworthy result of the last ten years, the direct outcome of studies of the mode of action of carcinogens, has been the recognition of the growth-inhibitory action of many tumour-producing agents. How this situation is only apparently paradoxical is explained in what follows, and the observation has in turn produced a good deal of interest in the nature of such inhibitory effects, and the extent to which they could form the basis of an experimental approach to chemotherapy. Meantime we have witnessed, in the control of carcinoma of the prostate by oestrogens, the first practical application of a drug in the treatment of at any rate one form of cancer—that the same oestrogens are capable of inducing a wide variety of tumours in other circumstances, is possibly more than a mere coincidence. This, of course, is only a token advance, but it will probably be the prelude to an entire series of similar discoveries (of which the action of urethane

and the nitrogen mustards are other examples), which should gradually accumulate until our whole outlook on the disease is transformed

Another unexpected development, which is only now being explored, holds out the prospect of an eventual rapprochement between the purely chemical interpretation of the origin of cancer and that other view which regards it as due to a process of virus infection. One of our contributors has speculated that disturbance of enzyme function, through the formation of a carcinogen-enzyme complex, could lead, by cellular adaptation, to the emergence of a new type of protein with auto-synthetic properties. A similar line of reasoning has developed from a recent observation that the growth-inhibitory effect of the carcinogens may be largely neutralized by incorporation in the diet of a sufficiently high proportion of protein, and the possibility—again still to be confirmed—that the carcinogens may function first of all by retarding protein-synthesis within the cell. These suggestive developments come at a time when quite independent advances in cytogenetics are shedding fresh light on the nature of viruses, and it will certainly be an astonishing outcome if the two contrasting and hitherto irreconcilable interpretations of the origin of cancer should be brought together in a common synthesis. This synthetic tendency, provided it is truly spontaneous and not artificially constrained to fit one or other particular viewpoint, is an encouraging feature of the subject at the moment, and is specially welcome as offering hope that the daily flood of facts, which we do everything in our power to encourage, will become progressively less a mere burden to the mind, and more a source of refreshment for the spirit!

This notice would be incomplete without mention of a different topic. The majority of the papers in the present number, and a good proportion of the advances they describe, are based on research carried out with the support and interest of the British Empire Cancer Campaign over more than twenty years. Through a wise policy of financial encouragement with freedom of investigation, the Campaign has achieved more than any other single body towards advancing the study of cancer in Britain. Not the least of its services has been the informal promotion of friendly contact and collaboration between active workers in numerous laboratories and institutions throughout the country, and the present number of the *Bulletin*, with papers by twenty authors

from eleven different centres in London, Oxford, Leeds, Manchester, Sheffield, and Glasgow, provides welcome evidence of the same good spirit.

Enough has been said to show that in spite of the inherent difficulties of the subject, and in spite of the meagre results which may attend the efforts of any individual worker, no matter how able or zealous, research in cancer continues to develop in the most interesting way, and to register steady progress. The effect is cumulative and a true advance once made is never lost, so that we now have a well-founded and growing structure of knowledge which would certainly surprise and gratify those who contributed to its modern beginnings. Assuming that our fundamental knowledge of cancer continues to grow, even at its current rate, developments are bound to occur which will bring practical benefits in the treatment of the disease in man. Extensive as our present knowledge is, it is likely that the greatest discoveries are yet to come. On the other hand, since it is those who work in the closest contact with the disease who are under the least illusion as to its refractory character, there is not, and there never was, the slightest ground for merely heedless or facile optimism. But we should also pay equal attention to the endless possibilities in the natural growth of science, in the face of which very few problems indeed are truly insoluble.

The attraction of this type of research is largely due to the scope which it offers to talents of the most diverse kinds. It combines the intellectual satisfaction which springs from fundamental work in biology, in chemistry, and in physics, with the mental satisfaction of contributing, even in small measure, to the alleviation of disease. It offers ample opportunity for teamwork, and equal opportunity to the individual worker and the man of ideas. It benefits from planned investigation, and also, as we have seen, from the play of chance. It demands more facts, yet not only facts but the capacity to produce a synthesis from such facts as we already have. We must not forget that the active investigation of cancer has been very largely confined to the past fifty years, and that research was conducted up to the first twenty or thirty years of the present century on only a very modest scale. The tempo is, however, steadily quickening, and while we are far from our objective no one can doubt, given a continuation of these fertilizing processes, that the greatest benefits must ultimately accrue.

PROFESSOR ALEXANDER HADDOW graduated in medicine in 1929, at Edinburgh, where he later became lecturer in bacteriology (1931-36). During this time he published a number of papers on special aspects of growth, such as the comparative pathology of tumours, viruses in relation to the etiology of cancer, and problems of immunity affecting the transplantation of tissues. Ever since his Edinburgh days, one of his main interests has been in bacterial mutation, and its importance in elucidating what he considers to be analogous problems of variation in the origin of cancer. In 1935, he described a growth-inhibitory property associated with carcinogenic compounds and has spent some years in developing this subject and relating it to the mechanism of action of tumour-producing agents generally. Recently he has been closely concerned with developments in chemotherapy, and is Vice-Chairman of the Joint Scientific Committee on Oestrogens in Cancer, of the British Empire Cancer Campaign and the Royal Society of Medicine. Professor Haddow's more recent papers deal with the transformation of cells and viruses (*Nature*, 1944, 154, 194), the artificial production of coat-colour by various *iso*-alloxazines (with L. A. Elson, K. M. Rudall, G. M. Timmis and E. M. F. Roe, *Nature*, 1945, 155, 379, *Endeavour*, 1945, 4, 141), and the action of urethane in leukaemia (with W. A. Sexton, E. Paterson and others, *Nature*, 1946, 157, 500, *Lancet*, 1946, 1, 677). He is at present engaged (with Professor G. A. R. Kon, F.R.S.) in a study of the growth-inhibitory and carcinogenic properties of derivatives of 4-aminostilbene. In 1946 he was appointed, in succession to Professor E. L. Kennaway, F.R.S., to the chair of experimental pathology in the University of London and the directorship of the Chester Beatty Research Institute of the Royal Cancer Hospital (Free).

PROFESSOR G. A. R. KON is an organic chemist who was for many years on the staff of the Imperial College of Science and Technology in London. His early researches dealt with problems of aliphatic and alicyclic chemistry, and some of them were devoted to the study of tautomerism. Later he became interested in the chemistry of the sterol group, and studied the problem mainly by the synthetic methods, soon afterwards he turned to the related field of the triterpenes, to the study of which he devoted many years. Since 1942 he has held the chair of chemistry at the Royal Cancer Hospital (Free), and in 1943 was elected a Fellow of the Royal Society.

DR I. BERENBLUM is a university demonstrator at the Sir William Dunn School of Pathology, and is in charge of the Oxford University Research Centre of the British Empire Cancer Campaign. Previously (1927-1936) he held the Riley-Smith Research Fellowship in the department of experimental pathology and cancer research at the University of Leeds. His published work includes papers and reviews on occupational tumours, on irritation in relation to the mechanism of carcinogenesis, and on various aspects of the application of micro-methods in the experimental study of cancer. His recent work (in collaboration with Dr R. Schoental) has been devoted to the study of carcinogenic constituents of tars and oils, and on the fate of chemical carcinogens in the animal body and the isolation of the products of their metabolism.

MR E. R. HOLIDAY is director of the spectrographic laboratory at the London Hospital. He has been interested for many years in the use of absorption spectrography as an analytical method and as a means of helping to establish the chemical structure of compounds of biological importance, e.g. Vitamin B₂ (*Ber. dtsch. chem. Ges.* 1934, 67, 1104, 1934, 67, 1352), purine glycosides (*Biochem. J.* 1930, 24, 619, *J. chem. Soc.* 1934, p. 1639, 1936, p. 765), proteins (*Biochem. J.* 1936, 30, 1795, 1938, 33, 1166), and polycyclic hydrocarbons (*Cancer Res.* 1943, 3, 151, 1943, 3, 686, 1946, 6, 699).

MR E. M. JOPE worked for some years in Oxford on the physico-chemical properties of blood-pigments and related porphyrin compounds (*Biochem. J.* 1945, 39, 239, etc.). He is now working in the spectrographic laboratory at the London Hospital, where, among other problems, the absorption spectra of polycyclic hydrocarbons and their derivatives are being studied. He is interested in the biochemical aspects of the development of erythrocytes, and has recently published new evidence concerning their destruction, from which their life-span can be estimated (*Brit. J. industr. Med.* 1946, 3, 136, *Proc. R. Soc. Med.* 1946, 39, 755).

MR H. G. CRABTREE studied organic chemistry at the University of Liverpool, and later specialized in colour chemistry at Leeds University. For the last 23 years he has been research chemist at the Imperial Cancer Research Fund, London, and has worked on problems connected with the chemotherapy of cancer, tissue-metabolism, effects of radiation on tissues and the mode of action of chemical carcinogens. He showed that the glycolysis which is characteristic of the cancer cell is a non-specific property shared by other pathological overgrowths (*Biochem. J.* 1928, 22, 1289), and demonstrated that short-wave radiations preferentially damaged the glycolytic mechanism of cells, when irradiation was carried out at low temperatures (*Biochem. J.* 1933, 29, 2334). This finding was used in an investigation of the influence of wavelength on the biological effectiveness of radiation (*Brit. J. Radiology*, 1939, 12, 39). More recently he has been concerned with the relation of sulphur metabolism to the initial phases of carcinogenesis. The demonstration that the carcinogenic process is retarded by a wide variety of substances which specifically, and by different chemical mechanisms, inhibit the functional activity of SH-groups, has led him to postulate that a primary stage in the action of chemical carcinogens is their fixation, through SH-linkages, to unknown cell-constituents.

DR F. DICKENS is Philip Hill professor of experimental biochemistry at the Courtauld Institute of Biochemistry, Middlesex Hospital School, University of London. Until recently, he was director of cancer research to the North of England Council of the British Empire Cancer Campaign, at King's College, Newcastle-upon-Tyne. He has now returned to the Courtauld Institute, where he was earlier (1923-1933) a research worker, for part of this period as a member of the scientific staff of the Medical Research Council. Professor Dickens has contributed to many aspects of tissue metabolism, especially to knowledge of the respiratory quotient of isolated tissue preparations. Applications of this work to the study of normal and tumour tissues have been described in a series of some twenty publications in the *Biochemical Journal* (1929-1941) and *Cancer Research* (1943, 3, 73). He recently (*Biochem. J.* 1941, 35, 1011) discovered the presence of considerable amounts of citrate in the hard substance of bone. Other work includes the application of ultra-short radio-waves to malignant tissues (*Amer. J. Cancer*, 1936, 32, 1626, 1645). Since 1938 he has been an editor of the *Biochemical Journal*, and he is the joint author with Professor E. C. Dodds of *The chemical and physiological properties of the internal secretions*, Oxford, 1925, and translator of O. Warburg's *Metabolism of tumours*, Constable, 1930.

DR E. BOYLAND is reader in biochemistry in the University of London at the Chester Beatty Research Institute of the Royal Cancer Hospital, where he has worked (except for the war years) since 1931. In addition to work on the metabolism of carcinogens he has worked with colleagues on the chemotherapy of cancer and on the nature of the carbohydrate metabolism of tumours. During the war he worked on problems of chemical warfare for the Ministry of Supply, and later on diseases of animals for the Ministry of Agriculture. Before starting cancer research, Dr Boyland worked in the physiological laboratory of the University of Manchester, the Lister Institute for Preventive Medicine, and the Kaiser-Wilhelm Institut für Medizinische Forschung in Heidelberg.

DR F. WEIGERT was lecturer in physical chemistry in Berlin and professor of photochemistry in Leipzig before coming to Britain. During his academic career he has studied the photochemistry of hydrocarbons, especially of anthracene and its derivatives. He discovered some specific effects of polarized light, and these researches established experimentally some theoretical photographic conceptions (Hurter & Driffield Lecture, *J. R. photogr. Soc.* 1938) and, especially since 1936 in Glasgow, a photochemical theory of colour vision (*Nature*, 1939, *Ophthalmologica*, 1940). A comprehensive survey of optical methods in chemistry was published as a book, *Optische Methoden der Chemie*, Leipzig, 1928. Since 1939, Dr Weigert has been research physico-chemist at the Mount Vernon Hospital, Northwood, Middlesex, where he is engaged in the study of the metabolism of carcinogenic hydrocarbons, especially benzpyrene, mainly with optical methods.

DR P R PEACOCK is the director of research at the Glasgow Royal Cancer Hospital. He was trained at Middlesex Hospital, London, where, after qualifying in 1924 he held resident appointments, and afterwards research scholarships in the Barnato Joel Laboratories until 1928. His early work was mainly concerned with fat soluble vitamins and with experimental radiology. He was appointed to his present post in 1928 and in 1933 became the Administrative Medical Officer at the same Hospital. He was appointed honorary lecturer in pathology to the University of Glasgow in 1943, and elected a Fellow of the Royal Faculty of Physicians and Surgeons of Glasgow in 1944. Dr Peacock's published work includes comparative studies of fowl sarcomas induced by chemical carcinogens and those spontaneous tumours that can be propagated by cell free extracts (*Amer J Cancer*, 1935, 25, 1, *Brit J exp Path* 1945, 26, 357, *Cancer Res* 1946, 6, 311). He has made a study of the metabolism of chemical carcinogens and described their natural routes of excretion (*Brit J exp Path* 1938, 19, 315, 434, *Brit J exp Path* 1940, 21, 227, *Biochem J* 1941, 31, 1276). He is particularly interested in dietary factors related to cancer of the alimentary tract. He holds the view that much human cancer could be avoided, and that closer co-ordination of clinical statistical and experimental research may lead to identification of some avoidable cases of cancer.

DR I HIEGER has been assistant in biochemistry in the Chester Beatty Research Institute of the Royal Cancer Hospital since 1924. He was a member of the team of workers which, under the inspired leadership of Kennaway, discovered the carcinogenic hydrocarbons and isolated 3,4-benzpyrene from pitch (Cook, J W, Hieger, I, Kennaway, E L & Mayneord, W V *Proc roy Soc B*, 1932, 111, 455, Hieger, I *Amer J Cancer*, 1940, 49, 496-504). During the last ten years he has been engaged on the investigation of carcinogenic agents in human tissue.

DR HAROLD BURROWS formerly practised as a consulting surgeon first in London and later in Portsmouth. During the 1914-1918 war he served as divisional surgeon at a hospital in France and became consulting surgeon to the First Army and later to the Army of the Rhine. He resumed civil life in 1919, but had to relinquish surgical practice a few years later because of ill-health, and has been occupied with research at the Royal Cancer Hospital in London since 1927. The Jacksonian Prize was awarded him in 1920 and he was a Hunterian professor in 1922, 1933, and 1935. His writings on surgery and research have been numerous and among his books are *Pitfalls of surgery*, 1925, *Some factors in the localization of disease in the body*, 1932 and *Biological actions of sex hormones*, 1945.

DR E S HORNING is a member of the scientific staff of the Imperial Cancer Research Fund Laboratories, London, NW7. Before joining the staff of the Fund he was a Rockefeller Foundation Fellow for medical research, and worked at the Kaiser-Wilhelm Institut, Berlin-Dahlem, and also at Washington University Medical School, St Louis, U.S.A., on problems dealing with experimental cytology. He was also a former Beit Memorial Fellow. Dr Horning has published numerous papers and several chapters for textbooks on cellular physiology, and also on the relationship of the sex hormones to carcinogenesis.

PROFESSOR E C DODDS occupies the Courtauld chair of biochemistry in the University of London. He has previously been the subject of a note (Volume IV, No 2) in the *Bulletin*, to which he contributed a review on morphine substitutes (*BMB* 818).

DR G M BONSER is Brotherton Fellow in cancer research in the University of Leeds. She has previously been the subject of a note (Vol IV, No 3) in the *Bulletin*, to which she contributed a review of knowledge on the genetics of cancer (*BMB* 876).

DR F BIELSCHOWSKY was a Privatdozent at the University of Freiburg and lecturer in Madrid on metabolic diseases before coming to Britain. Since 1939, he has been working in the department of pathology of the University of Sheffield. After

collaborating with Professor H N Green in an investigation of the mode of action of sulphanilamide (*Brit J exp Path* 1942, 23, 1, 23, 13), he began in 1942 to work on problems of cancer studying the action and the metabolism of aromatic amines. His earlier work dealt with problems of the metabolism of nucleic acids and of lipoids. Dr Bielschowsky is a member of the Biochemical Society and of the Pathological Society of Great Britain and Ireland.

DR J W ORR is reader in experimental pathology and assistant director of cancer research in the University of Leeds. He was previously first assistant pathologist at St Mary's Hospital, Paddington. He is a graduate of the Queen's University of Belfast and has had wide experience in general pathology more particularly in morbid anatomy. He has published papers on a variety of pathological subjects, his more recent work being largely concerned with problems of experimental cancer research. He has made investigations on the action of many chemical carcinogenic substances including *p*-dimethylaminoazobenzene, one of the most important of the liver carcinogens. Unfortunately, for a variety of reasons, his work on experimental liver cancer (with L H Stuckland) had to be abandoned during the war but is now being resumed.

DR S A HENRY was educated at Trinity College, Cambridge and St Thomas's Hospital, London. After some years in general practice he became, in 1920, a medical inspector of factories in the Factory Department of the Home Office under the late Sir Thomas Legge, whose posthumous work on *Industrial maladies* he edited as requested in Sir Thomas's will. He retired from the Factory Department in 1944. He is an authority on industrial diseases especially industrial cancer, and has published numerous papers on these subjects. He was appointed Secretary to the Home Office Departmental Committee set up in 1925 to investigate the causes of cancer of the scrotum. In 1940, as Hunterian Professor, he lectured at the Royal College of Surgeons on *Cancer of the scrotum in relation to occupation*. In 1943 he delivered two Milroy lectures at the Royal College of Physicians on the *Health of the factory worker in wartime*, and in 1944 a Chadwick lecture on *Medical supervision in industry in peace and war*. Dr Henry is the author of a monograph entitled *Cancer of the scrotum in relation to occupation*, Oxford, 1946, which is reviewed elsewhere in these columns.

DR A N CURRIE is His Majesty's Medical Inspector of Factories in charge of the Central Metropolitan Division, London. He has served as a medical inspector for 16 years—2 in Sheffield, 11 in Glasgow and 3 in London. This work afforded ample opportunity of studying occupational cancers, and he made a special study of cancer of the urinary bladder among dyeworkers in the Midlands of England. In the past Dr Currie was a lecturer in industrial hygiene in the Universities of Glasgow and St Andrews. Before entering government service, he was biochemist to the Royal Cancer Hospital, Glasgow, and carried out considerable research work with the late Sir George Beatson on the role of fat, lipochrome and cholesterol in the etiology of cancer. Dr Currie is a member of the Association of Industrial Medical Officers. His publications include 'The lipochrome of adipose tissue in malignant disease' (*Biochem J* 1924, 18, 235), 'The cholesterol of blood in malignant disease' (*Brit J exp Path* 1924, 5, 293), 'Chemical haematuria from handling 5-chloro-ortho-toluidine' (*J industr Hyg* 1933, 15, 205), and various papers on occupational diseases read to learned societies.

DR M W GOLDBLATT is Division Medical Officer to Imperial Chemical Industries Ltd. He was formerly lecturer in physiology at St Thomas's Hospital, London, and a Beit Memorial Fellow. He is a member of the Advisory Committee on Industrial Health to the Ministry of Labour and of the Editorial Committee of the *British Journal of Industrial Medicine* and of the Industrial Health Committee of the British Medical Association. He is lecturer in industrial health in the University of Manchester, and a member of the Biochemical and Physiological Societies. He has published papers on the physiological action of hormones and on toxic hazards in industry.

CHEMISTRY OF CARCINOGENIC COMPOUNDS

ALEXANDER HADDOW, M D, D Sc, Ph D
G. A R KON, M A, D Sc, F R S

Chester Beatty Research Institute, Royal Cancer Hospital (Free), London

- 1 Nature of the carcinogenic agent in coaltar and pitch
 - 2 Benzantracene homologues
 - 3 Chrysenes and benzphenanthrenes
 - 4 Possible implications for the spontaneous origin of cancer
 - 5 Oestrogens and cancer
 - 6 Nitrogen- and sulphur-containing analogues, 2-amino derivatives of naphthalene, anthracene and fluorene
 - 7 Azo compounds
 - 8 Derivatives of 4-aminostilbene
 - 9 Miscellaneous substances radioactive elements, arsenic, urethane
- References

That scientific progress is equally dependent upon natural observation and planned experiment is nowhere more richly illustrated than in the early history of carcinogenesis. For all practical purposes, the story began when Percivall Pott (1713-88), who was surgeon to St. Bartholomew's Hospital, and who was aware of and interested in Ramazzini's accounts of the *morbi artificum*, described a particular form of cancer occurring in chimney-sweeps (cancer scroti, in *Chirurgical observations*, 1775), and traced it to a specific cause, namely contamination of the skin by soot. Other examples of this curious disease continued to be reported from time to time by a long line of English surgeons, including Earle, Astley Cooper, Hughes Bennett, Paget, and Butlin. For various reasons it appears not to have been observed to any great extent abroad (*verruë de soie, cancer des ramoneurs, Schornstefegerkrebs*), but was sufficiently frequent in Britain to make a tragic addition to the already miserable plight of the so-called "climbing boys", and to find a reflection in the social history and legislation of the time.

The interest of the condition clearly lay in the proof which it brought of the environmental origin of at any rate one form of cancer, and this by itself would no doubt have provided a sufficiently powerful stimulus to later investigators. However, in the second half of the nineteenth century there appeared other and fresh accounts of cancer as an industrial hazard. Thus, in 1875, von Volkmann discovered occupational skin-tumours among the workers in the tar and paraffin industry at Halle. In the following year, the celebrated Joseph Bell of Edinburgh described the earliest cases in the Scottish shalefield of "paraffin cancer", the natural history of which was to be so admirably related by Alexander Scott (1923) almost fifty years afterwards. Still later, in 1887, was found the first example of skin cancer affecting operatives in the Lancashire cotton-spinning industry, and now known to be attributable to occupational

contact with mineral oil used in lubrication—the so-called "mule-spinners' cancer".

All these phenomena were the results of undesigned and unpredictable "natural" experiments on a grand scale—the unforeseen outcome of one or other aspect of the current industrialization. How frequent such environmental experiments have been and still are, and how fascinating in their variety, may be judged from Dr Henry's (1947) account¹ of cutaneous cancer attributable to chemicals in industry. The next stage was clearly that of systematic inquiry, and the first essential lay in the reproduction of the disease at will. One of the earliest attempts was made by Hanau in 1889. Inspired by von Volkmann's paper, he tried to induce cancer in rats and dogs by painting the skin "mit Hallenser Braunkohlen theer", but without result. Success proved tardy, just eluding Bayon in Britain in 1912, but was finally achieved by Yamagiwa & Ichikawa in 1915, when they produced undoubted malignant epithelial tumours by application of coaltar to the ears of rabbits. In 1918 Tsutsui (a pupil of Yamagiwa) showed the advantage of painting the skin of mice as a method of biological testing of carcinogenic tars—a simple technical variation which was nevertheless to have a profound influence upon all later developments. In 1922, strict proof of the carcinogenicity of soot was obtained when Passey produced malignant growths by painting the skin of mice with an ethereal extract.

¹ [BMB 976]

FIG 1



FIG 2



Wellcome Historical Medical Museum

Katsusaburo Yamagiwa 1863-1930

1 Nature of the Carcinogenic Agent in Coal-tar and Pitch

Possibly the first usage of the term carcinogen was by Sir James Paget in 1853, in a somewhat obscure passage in his classic *Lectures on surgical pathology*

" is there one material for cancer, one *carcinogen* which, like an organic radical, may form different yet closely allied compounds, in its combinations with the various substances provided by different bloods, or different parts ? "

All the above facts had very clearly shown the existence of at least one such cancer-producing agent, and the stage was now set to elucidate its precise nature in chemical terms. There is a remarkable sentence in Lebert's *Traite pratique des maladies cancéreuses* (1851) in which the famous author shows a high degree of prophetic insight into the conditions required for the necessary progress

" Il faut que, pour un pareil travail, un homme profondément versé dans la connaissance anatomique et pathologique du cancer se réunisse à un chimiste qui, de son côté, soit au courant des progrès les plus récents de la science "

The first-fruits of this union came relatively late, in 1921-26 with a demonstration by Bruno Bloch and Dreifuss and their collaborators in Zürich that the active substance of coal-tar was concentrated in the higher boiling fractions as a neutral compound and the recognition that this was free from nitrogen, arsenic or sulphur, was capable of forming a stable

complex with picric acid, and probably belonged to the class of cyclic hydrocarbons (Bloch & Dreifuss, 1921)

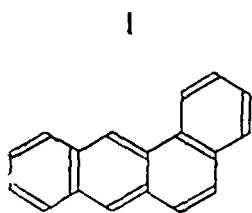
In 1924 and 1925 Kennaway succeeded in producing carcinogenic tars by the pyrolysis of petroleum, coal, skin hair, yeast and cholesterol, and by leading acetylene and isoprene— $\text{H}_2\text{C}=\text{C}(\text{CH}_3)\text{CH}=\text{CH}_2$ —with hydrogen through strongly heated tubes. The tars so obtained showed an ascending order of biological potency according as they were prepared at successively higher temperatures (450-1,250° C) and these results could be explained by assuming that acetylene was a common decomposition-product, and that the carcinogenic material was actually formed from acetylene. Similar activity was found by Kennaway (1924, 1925) in the higher-boiling fractions of the mixture of hydrocarbons which Schroeter (1924) had obtained from tetrahydronaphthalene by treatment with aluminium chloride. There thus emerged, gradually but surely, the strong general conclusion that the carcinogenic agent was a complex hydrocarbon of the aromatic series.

Since the carcinogenic tars and oils usually showed a pronounced fluorescence, Mayneord in 1927 examined their fluorescence-spectra, and discovered them to possess a characteristic spectrum consisting of three bands at low dispersions. This quite vital clue was developed by Hieger (1930) in an investigation of the fluorescence of a number of polycyclic aromatic hydrocarbons, particularly those related to anthracene. It may be noted here how necessarily dependent were such investigations upon the parallel development of chemistry in general, and upon the chemistry of the aromatic hydrocarbons in particular. As only one of many examples may be mentioned, Chattaway's earliest work with Bamberger at München, which resulted in the determination of the constitution of a number of polynuclear hydrocarbons which occur in minute quantity in the highest-boiling fractions of coal-tar.

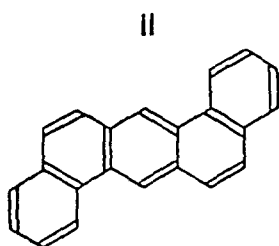
If however our knowledge of cancer was dependent upon chemistry—as it still is and to an ever-increasing extent—chemistry itself was soon to gain much in return from the stimulus of developments in the following years. By a most fortunate chance, the known pure compounds which Hieger proceeded to examine included 1,2-benzanthracene (I) and this substance was at once found to give a spectrum comparable with that of the carcinogenic mixtures. It was this circumstance which shortly led Cook to embark on the long series of synthetic studies on homologues of benzantracene (Cook, Hieger, Kennaway & Mayneord 1932) which founded our knowledge of the structural features underlying carcinogenic action, at any rate so far as this type of compound is concerned. About this time Erich Clar (1929) had just published a series of methods for the synthesis of certain slightly more complex hydrocarbons containing the benzanthracene system. These substances were at once tested for carcinogenic activity by Kennaway & Hieger (1930), who soon obtained positive results with the compound ultimately identified as 1,2,5,6-dibenzanthracene (II). This was therefore the first known pure chemical compound manifesting pronounced carcinogenic properties.

The fluorescence-spectrum—in Kennaway's words "the single thread that led all through this labyrinth"—and as can be seen from the contribution² of Berenblum, Holiday & Jope (1947), still an invaluable physical technique for the investigation of the carcinogenic hydrocarbons—was also

¹ [BAM 963]

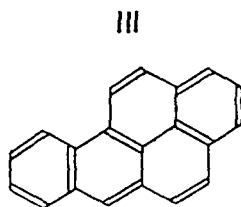


I 2-benzanthracene



I 2 5 6-dibenzanthracene

used by Hieger (1933) in the concentration of the carcinogenic agent from coaltar pitch, culminating in the isolation of a pure hydrocarbon which showed the characteristic three-banded spectrum, and which proved to be strongly carcinogenic. At the time of its isolation this compound had not been elsewhere recorded, and it was therefore necessary to determine its molecular structure. Its properties suggested one of the two possible benzpyrenes, and these were synthesized by Cook & Hewett (1933), who were soon able to prove the identity of one of the compounds (3,4-benzpyrene, III) with the substance isolated from pitch. Tedious as the early extractions necessarily were, it was subsequently found by Berenblum & Schoental (1943), using a spectrographic method of estimation, that tar might contain as much as 1.5% of benzpyrene, and Berenblum has more recently devised (1945) a relatively simple procedure (starting from the fact that sulphonation of benzpyrene does not readily occur with sulphuric acid alone in the cold), whereby as much as 75 mg of almost pure benzpyrene can be recovered from 10 g of a crude tar distillate.



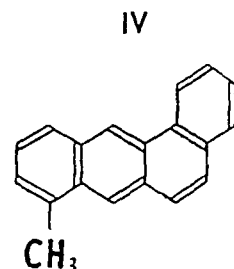
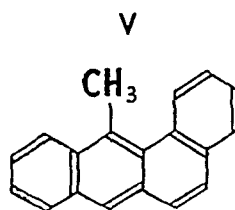
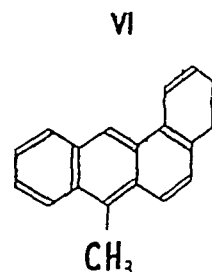
3, 4-benzpyrene

2 Benzanthracene Homologues

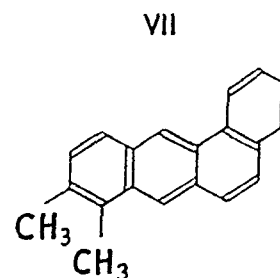
Cook's (Barry, Cook, Haslewood, Hewett, Hieger & Kennaway, 1935) study of the benzanthracene homologues first disclosed the great significance of position 5 in the parent hydrocarbon, whereas benzanthracene itself is non-carcinogenic or only very weakly active, methyl substitution in this position confers a high order of potency (IV). This is probably a factor underlying the activity shown by compounds in which an additional ring finds one point of attachment in the same position, as, for example, in 1,2,5,6-dibenzanthracene (II). It was later shown that methyl substitution in positions 9 or 10 (V, VI) also leads to highly carcinogenic compounds, and indeed 10-methyl-

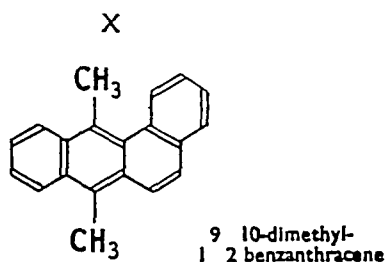
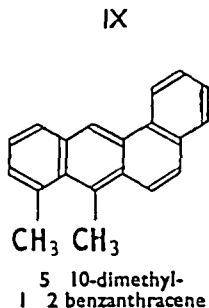
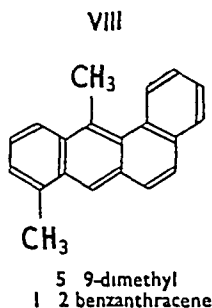
1,2-benzanthracene is the most active of all the monomethyl derivatives of the parent compound. Of the remaining monomethyl isomerides, only the 6-methyl-derivative exhibits notable activity, the others little or none.

Proceeding to dimethyl-benzanthracenes, an important conception emerged when it was shown that substituents at any two favourable positions reinforce each other, so that the activity of the new compound is enhanced. Thus

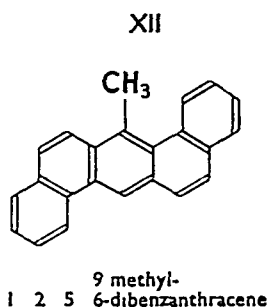
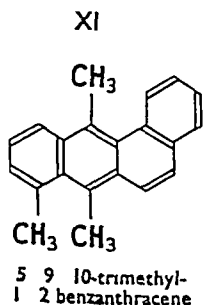
5-methyl-
I 2-benzanthracene9-methyl-
I 2-benzanthracene10-methyl
I 2 benzanthracene

5,6-dimethyl-1,2-benzanthracene (VII) is more active than the compounds possessing only one methyl group in position 5 or 6, high activity is shown by 5,9- and 5,10-dimethyl-1,2-benzanthracene (Fieser, 1936) (VIII, IX), and extreme potency is reached in 9,10-dimethyl-1,2-benzanthracene (Bachmann, Kennaway & Kennaway, 1938) (X).

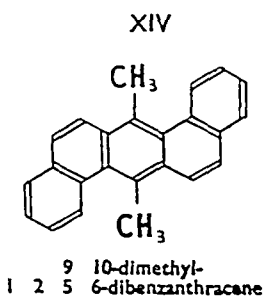
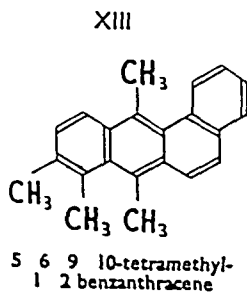
5 6-dimethyl-
I 2-benzanthracene



It is possible that still greater augmentation is effected by methyl substitution simultaneously in *three* favourable positions as in 5 9 10-trimethyl-1 2-benzanthracene (XI) and 9-methyl-1 2 5 6-dibenzanthracene (XII)

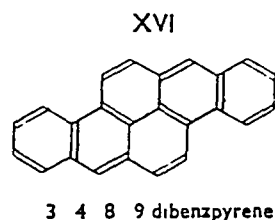
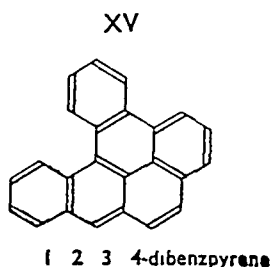


There is a limit to advance in potency by increase in number of substituted positions since the compounds in which the four most favourable are substituted (5 6 9 10-tetramethyl-1 2-benzanthracene (XIII) and 9 10-dimethyl-1 2 5 6-dibenzanthracene (XIV) show *decreased* activity as compared with XI and XII. Furthermore, increase in the alkyl-chain length at positions 5 or 10 leads to decline of

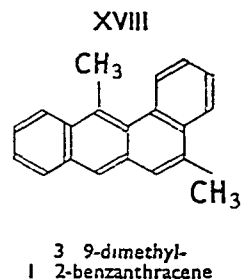
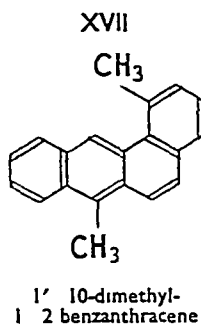


activity which is slow in the first position (to *n*-heptyl) and much more rapid in the second

These facts at once suggest the dependence of activity on an optimal molecular complexity, a conclusion which Cook (Barry *et al*, 1938) had stressed at an early stage in these investigations, and which is upheld by many later examples. The limits of complexity compatible with activity are represented by two hexacyclic hydrocarbons, 1 2 3 4- and 3 4 8 9-dibenzpyrene (XV XVI)



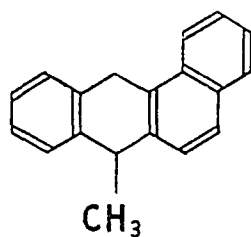
Apart from cases in which activity is reduced, apparently by increase in molecular size or complexity, one or two examples may be quoted in which substitution in a position in itself not favourable to activity, or only slightly so, simultaneously with substitution in a favourable position greatly reduces the activity due to the latter. Two remarkable cases are seen in the inactive compounds 1' 10-dimethyl-1 2-benzanthracene and 3 9-dimethyl-1 2-benzanthracene (XVII, XVIII) [Compare the active isomerides (IX) and (VIII) respectively]



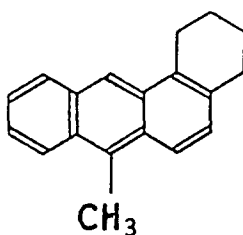
The nature of the substituent is also capable of variations compatible with activity as in many compounds with oxygen-, nitrogen- and halogen-containing groups mostly in positions 10, 9 and 5 in 1 2-benzanthracene. As might be expected however [cf the article³ in this number by Boyland & Weigert (1947)] introduction of phenolic groups usually entails complete loss of carcinogenicity and it is a general rule though not quite an invariable one, that the same result follows the hydrogenation of individual rings. Examples of the latter are shown in the inactive compounds XIX XX and XXI

³ [BMB 968]

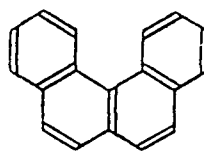
XIX

9,10-dihydro-10-methyl-
1,2-benzanthracene

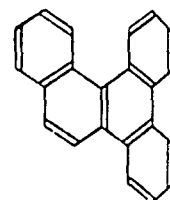
XX

1',2',3',4'-tetrahydro-
10-methyl-1,2-benzanthracene

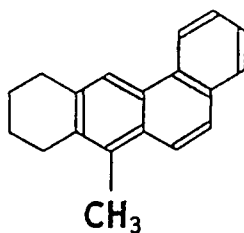
XXIV

3,4-
benzphenanthrene

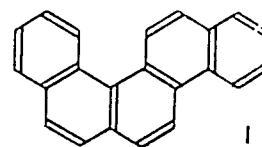
XXV

1,2,3,4-
dibenzphenanthrene

XXI

5,6,7,8-tetrahydro-
10-methyl-1,2-benzanthracene

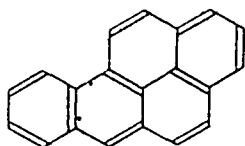
XXVI

1,2,5,6-
dibenzphenanthrene

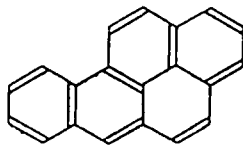
3. Chrysenes and Benzphenanthrenes

Many of the cases quoted above permit some degree of analogy with derivatives of 3,4-benzphenanthrene and chrysene, and it may be recalled that while Cook (Cook & Hewett, 1933) regarded 3,4-benzpyrene as most-nearly related to 1,2-benzanthracene (as in XXII), for other reasons Fieser (1941) suggested it should more suitably be formulated as a chrysene derivative (as XXIII).

XXII



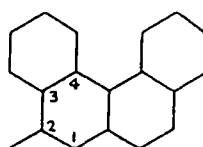
XXIII



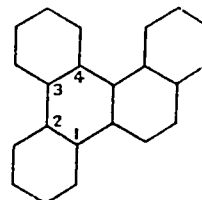
Marked progress was achieved on complete examination of the 6 possible hydrocarbons consisting of 4 condensed aromatic rings, and of the 15 compounds having 5 such rings. This revealed carcinogenic activity in 3,4-benzphenanthrene (XXIV) and in 1,2,3,4- and 1,2,5,6-dibenzphenanthrene (XXV, XXVI), and it also appeared that chrysene, as well as 1,2-benzanthracene and 3,4-benzphenanthrene, must be regarded as a parent compound of carcinogenic derivatives. The next stage in this fascinating correlation was due to Hewett (1940). Each of these hydrocarbons is a derivative of phenanthrene, substituted in two of the 1-, 2-, 3- and 4-positions. Further substitution in either or both of the remaining positions gives rise to highly carcinogenic hydrocarbons (e.g. 2-methyl-3,4-benzphenan-

threne (A), 1,2,3,4-dibenzphenanthrene (B), 1,2-dimethylchrysene (C), 3,4-benzpyrene (D), 9,10-dimethyl-1,2-benzanthracene (E). Moreover, substitution is effective whether by two benzene rings or by one benzene ring and one or two methyl groups, this finally led Hewett & Martin (1940) to the synthesis of 1,2,3,4-tetramethylphenanthrene (F)—a key compound which is slightly carcinogenic, links the active derivatives of 1,2-benzanthracene, 3,4-benzphenanthrene and chrysene, and may be regarded as the prototype of all these compounds.

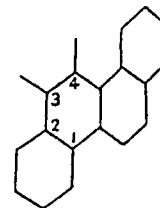
A



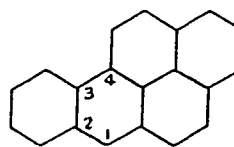
B



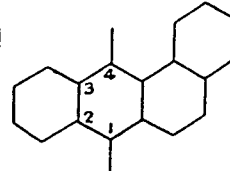
C



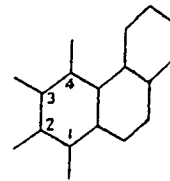
D



E



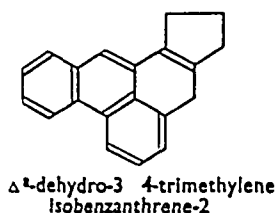
F



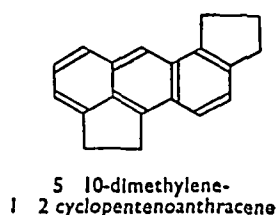
(Numbering indicates relation to phenanthrene)

Even the phenanthrene nucleus is not indispensable, since activity is marked in structures XXVII and XXVIII and in certain dibenzfluorenes (e.g. XXIX and XXX), and is detectable in as simple a compound as 9,10-dimethylanthracene (XXXI).

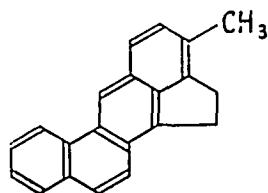
XXVII



XXVIII

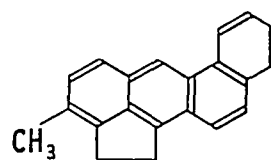


XXXIVa



20-methylcholanthrene

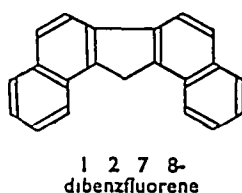
XXXIVb



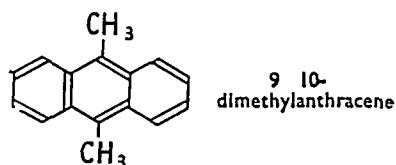
XXIX



XXX



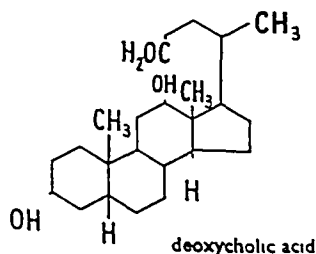
XXXI



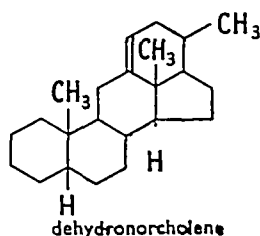
4 Possible Implications for the Spontaneous Origin of Cancer

Thus far, the clues drawn from industrial skin cancer had led to the chemical identification of the substance responsible, and to the discovery of other aromatic hydrocarbons, mostly related to benzantracene, and possessing carcinogenic properties. The possibility that such compounds might play a part in the causation of "spontaneous" cancer was opened up by recognition, following the advances in sterol formulation due to Rosenheim & King in 1932, that many naturally-occurring compounds (including bile-acids and the sex hormones) have somewhat similar condensed polycyclic systems. Thus dehydronorcholene (XXXIII), a hydrocarbon prepared by Wieland & Schlichting from the bile-acid deoxycholic acid (XXXII), is a hydro-derivative of 1,2-benzanthracene, and in 1933 both Wieland & Dane, and Cook & Haslewood, obtained from it, by dehydrogenation with selenium, the fully-aromatic hydrocarbon methylcholanthrene (XXXIVa or b).

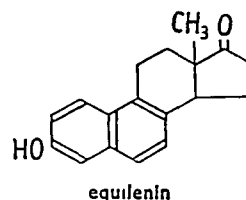
XXXII



XXXIII



XXXV



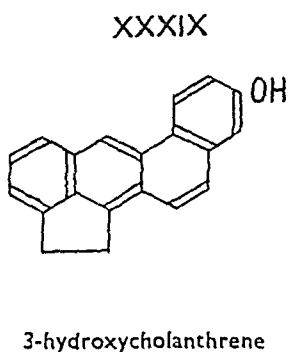
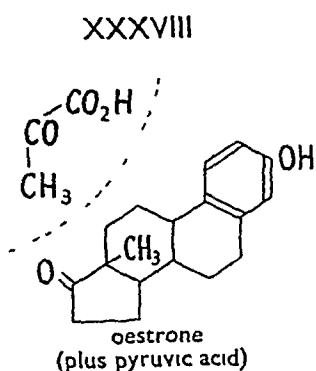
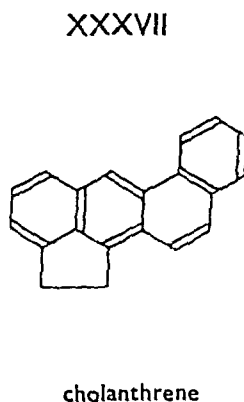
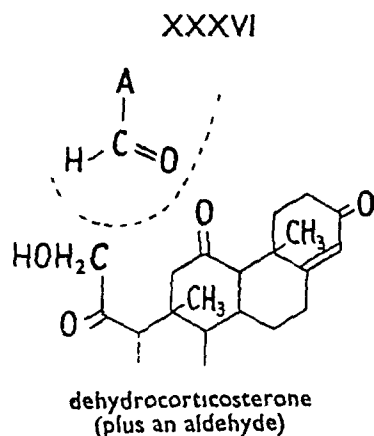
This compound soon proved to have carcinogenic potency of an extremely high order—as Cook (1933) had indeed predicted. The structure was rapidly established and confirmation provided by its synthesis (Fieser & Seligman, 1935) and the compound was also obtained starting from cholic acid (Fieser & Newman, 1935).

There is as yet no proof that changes of the kind envisaged take place *in vivo*, and chemists are still divided as to their likelihood. Both cholic acid and deoxycholic acid have a hydroxyl group in such a position (Kennaway & Hieger, 1930) as would promote the necessary cyclization of the side-chain. Further, from other cases in which there was no such special circumstance to favour ring-closure, Cook was of opinion that certain sterol molecules might possess an inherent tendency to conversion into a methylcholanthrene derivative. However, as has already been indicated, marked carcinogenic activity is not generally found in compounds possessing hydrogenated rings, so that a further stage of dehydrogenation would be required. Important here is a finding by Ghuron, confirmed by Kennaway (Cook, Kennaway & Kennaway, 1940) that injection of deoxycholic acid itself may result in the production of connective-tissue tumours in mice. In such a case it would be of interest to know—although it is difficult to tell how the question might be solved—whether deoxycholic acid is intrinsically active or is subject to a transformation *in vivo* yielding traces of an active product. One of the best analogies for the conversion of a hydrogenated ring-system into an aromatic one is provided by the oestrus-producing hormone equilenin (XXXV), possessing two aromatic rings and probably arising from a non-aromatic steroid precursor (Sandulesco, Tchung & Girard, 1933, Fieser 1941).

It may be noted in passing, as having an important bearing on the biogenesis of the steroids—whether, for example cholesterol is the precursor of the bile-acids and sex hormones, or whether biosynthesis may proceed from three-carbon sugars after the hypothesis of Reichstein, or by a scheme involving tyrosine according to Robinson's suggestion—that Bloch (1945) has recently adduced evidence of

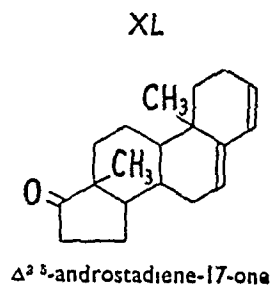
direct conversion of cholesterol to progesterone as a normal process, through administration of deuteriocholesterol to a pregnant woman, and isolation from the urine of sodium pregnanediol glycuronide containing concentrations of the isotope indicating that two-thirds of the progesterone metabolized arose by degradation of cholesterol.

In Fieser's (1941) view the rough structural analogy between equilenin and methylcholanthrene suggests that, if the latter does indeed arise by a process of abnormal sterol metabolism, this process may be closely associated with the normal one which results in the production of oestrogenic hormones. He, therefore, invited consideration of the production of carcinogens from the principles of the adrenal cortex, visualizing such reactions as might ensue from the condensation of dehydrocorticosterone (XXXVI) with formaldehyde to give cholanthrene (XXXVII), and of oestrone (XXXVIII) or equilenin with pyruvic acid, followed by aromatization, ring-closure to give the terminal benzenoid nucleus and further dehydrogenation.

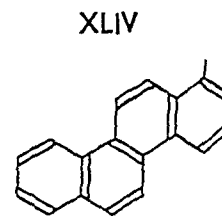
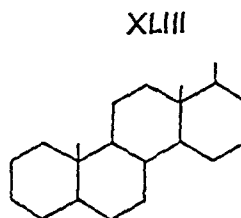
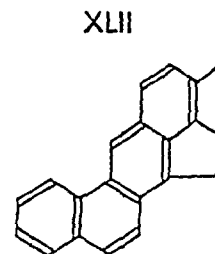
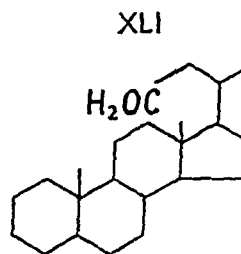


A difficulty arises here (as also for deoxycholic acid above), since the product, because of the persistence of the original hydroxyl group at C₃ characteristic of all known natural partially-aromatic oestrogens, would be a 3-hydroxy derivative (XXXIX) and therefore unlikely to be carcinogenic on analogy with the known inactivity of the synthetic compound 3-hydroxy-20-methylcholanthrene. A highly relevant observation was, however, made by Burrows, Cook, Roe & Warren (1937) when they isolated from the urine of a male with an adrenal tumour a substance— $\Delta^3,5$ -androstadiene-17-one (XL)—lacking this characteristic 3-hydroxyl group, and

so showing that the C₃-hydroxyl may in certain circumstances be eliminated while the ring-system is still non aromatic. The same compound was later isolated by Wolfe (Wolfe, Fieser & Friedgood, 1941) in Fieser's laboratory, from the urine of a female with adrenal tumour.



Shopee (personal communication) points out that the structural analogy between a norcholanic acid (as XLI) and methylcholanthrene (XLII) is paralleled by the even closer analogy between 17-methyl-D-homoandrostane (XLIII) and the carcinogenic methylchrysenes (as XLIV), and Fieser's



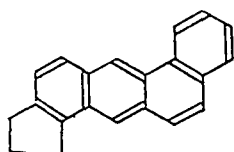
(1941) opinion that the cortical steroids seem the more likely precursors of possible carcinogens *in vivo*, has a very particular significance for the remarkable case of the CE strain of mice, in which either ovariectomy or castration shortly after birth leads to the development of adrenal-cortical carcinomata—conceivably arising from a response on the part of the adrenal to compensate for the absence of the gonads (Fekete & Little, 1945). This phenomenon is considered in detail in the article⁴ in this number by Burrows & Horning (1947) and it should also be noted that Woolley & Little (1946) have more recently described the prevention of adrenal cortical carcinoma by the synthetic oestrogen diethylstilboestrol.

5 Oestrogens and Cancer

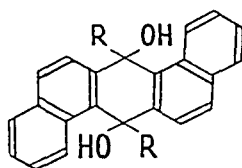
The above account is sufficient to indicate the remarkable way in which the structure of purely extraneous carcinogens and even more of synthetic variants which we have no reason

to believe have ever existed under natural conditions can nevertheless provide indications both of a certain affinity with substances of importance in the animal economy, and of the means by which fully aromatic carcinogens might conceivably be formed as a result particularly of some local disturbance of sterol metabolism. A more direct connection between carcinogenesis and a physiologically important molecule was discovered by Lacassagne in 1932, when he found that injection of the female sex hormone produces cancer of the breast in male mice, under certain favourable conditions. We now know that the appearance of breast cancer in mice is determined by a number of predisposing and conditioning factors. Also, the carcinogenic action of the oestrogens is mainly confined to tissues which are highly responsive to their physiological action. Nevertheless Lacassagne's experiment was the first in which cancer was produced by a naturally-occurring compound. To what extent this subject has ramified is shown by Burrows & Horning's (1947) article⁴ on oestrogens and neoplasia, with its detailed accounts of the production of pituitary, mammary uterine, testicular, adrenal, subcutaneous leukotic and osseous tumours in mice and other species with both natural and synthetic oestrogens. About the time of Lacassagne's original observation Cook & Dodds (1933) showed that individual synthetic compounds—e.g. 5,6-cyclopenteno-1,2-benzanthracene (XLV) and 3,4-benzpyrene (III)—might show slight oestrogenic as well as carcinogenic activity and oestrogenic action was also discovered in certain dialkyl derivatives of 1,2,5,6-dibenz-9,10-dihydroanthraquinol (XLVI).

XLV

5,6-cyclopenteno-
1,2-benzanthracene

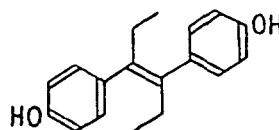
XLVI

di alkyl-
dibenzanthracene diols

This work soon led to larger-scale researches by Dodds and Robinson and their collaborators (Dodds, Goldberg, Lawson & Robinson, 1938), and to the synthesis of artificial oestrogens of extraordinary potency. Among such compounds discovered later diethylstilboestrol (XLVII) and triphenylethylene (Robson & Schonberg, 1937) (XLVIII) are now known to be specially capable of inducing breast- and testis-tumours in mice of susceptible strains. These structures should be compared with oestrone (XLIX) and chrysene (L) and it may be noted that triphenylethylene may also be formulated as a phenanthrene derivative with one ring disrupted or possibly as a benzanthracene system with two rings disrupted.

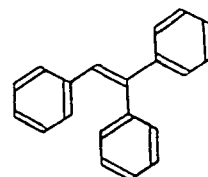
⁴ (BMB 971)

XLVII



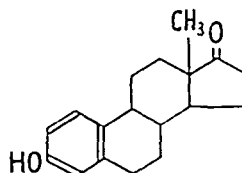
diethylstilboestrol

XLVIII



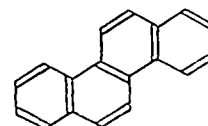
triphenylethylene

XLIX



oestrone

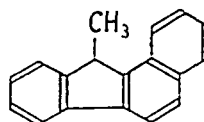
L



chrysene

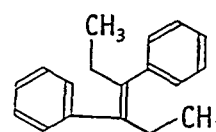
So far as polycyclic aromatic compounds are concerned by far the highest oestrogenic activity yet encountered was observed by Haddow & Badger (unpublished) in 9-methyl-1,2-benzfluorene. In a closely-related series of benzfluorenes, oestrogenic action was specific to this individual compound, a fact which may be related to its schematic similarity to diethylstilbene, as shown in LI and LII.

LI



9 methyl 1,2 benzfluorene

LII

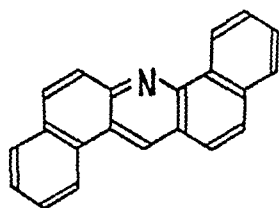


diethylstilbene

6 Nitrogen- and Sulphur-containing Analogues 2-Amino Derivatives of Naphthalene, Anthracene and Fluorene

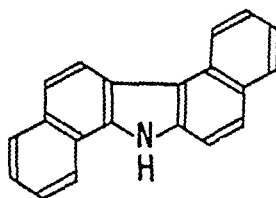
Carcinogenicity is by no means restricted to cyclic hydrocarbons for it is found in certain nitrogenous analogues such as dibenzacridines and dibenzcarbazoles (e.g. LIII, LIV). Lacassagne, Rudali, Buu-Hoi & Lecocq (1945) and Lacassagne (1946) have recently devoted attention to a series of methylated derivatives of the angular benzacridines (LV, LVI) and find a marked distinction in that such derivatives of 1,2-benzacridine include many highly potent compounds while similar derivatives of 3,4-benzacridine are for the most part inactive.

LIII



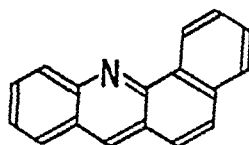
1 2 5 6-dibenzacridine

LIV



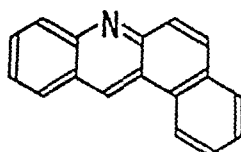
1 2 5 6-dibenzcarbazole

LV



1 2-benzacridine

LVI

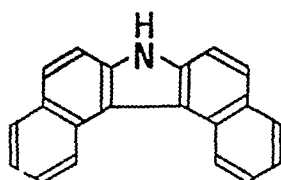


3 4-benzacridine

Some years ago, Boyland (Boyland & Brues, 1937) directed special notice to 3,4,5,6-dibenzcarbazole (LVII), on account of its possible formation from 2-naphthylamine (LVIII), one of the intermediates believed to be responsible for occupational cancer of the bladder in dye-workers (Rehn, 1895), and now known to be able to induce this disease experimentally in dogs (Hueper, Bonser)⁵. 3,4,5,6-Dibenzcarbazole has the property of inducing tumours not only locally, but in the liver as well, and this type of carcinogenic action at a distance is found to be thoroughly characteristic of many such nitrogenous analogues, in contrast with the polycyclic hydrocarbons, the effects of which are more usually confined to the point of application or injection. The effects of methylation on the carcinogenic activity of 3,4,5,6-dibenzcarbazole has recently been the subject of a special study by Kirby & Peacock (1946)

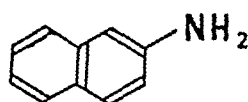
2-Naphthylamine is in turn related to 2-anthramine (LIX), which was originally observed by Shear (1938) to produce

LVII



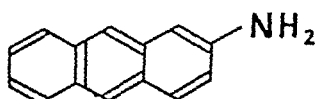
3 4 5 6-dibenzcarbazole

LVIII



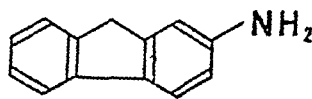
2-naphthylamine

LIX



2-anthramine

LX

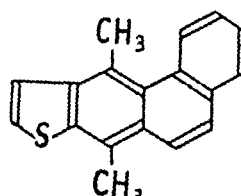


2 aminofluorene

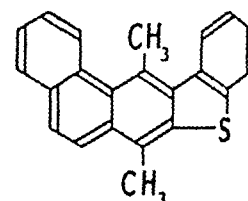
multiple hepatomas in mice, and this to 2-aminofluorene (LX), the acetyl derivative of which was discovered by Wilson, De Eds & Cox (1941), following its use as an insecticide, to possess carcinogenic activity of an exceptionally diversified type. The capacity of 2-acetylaminofluorene to produce such varied growths as squamous keratinizing carcinomata, basal cell carcinomata, mammary cancer, adenomata and carcinomata of the lung, benign and malignant tumours of the liver, and tumours of the bladder and kidney, has been sufficiently described in this number by Bielschowsky⁶ (1947), and no further reference need be made to this subject here

Finally, as additional examples of the manner in which the polycyclic hydrocarbon pattern can be modified, while still retaining carcinogenic potency, may be quoted the compounds LXI (Sandin & Fieser, 1940) and LXII (prepared by Tilak, 1946), in each of which a benzene ring of the 9,10-dimethyl-1,2-benzanthracene system is replaced by a thiophene nucleus

LXI



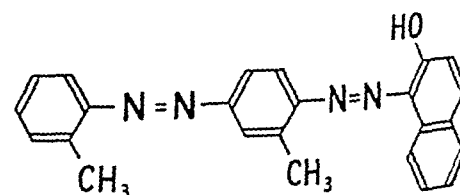
LXII



7 Azo Compounds

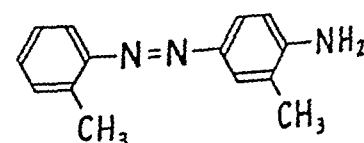
Of the remaining chemical carcinogens, a great number fall in the class of azo compounds. As early as 1906, B. Fischer described epithelial proliferation (in the ears of rabbits) following the injection of scarlet red (Biebrich Scarlet R medicinal) (LXIII). Although the growths were non-malignant, Fischer rightly claimed his discovery as the first case of the induction of tumour-like proliferation by a chemical compound. A few years later, Hayward (1909) found that the active part of the scarlet-red molecule was represented by 4'-amino-2,3'-azotoluene (LXIV). Scarlet red was also used by Yamagiwa, but his success in producing malignant growths by coal-tar seems to have diverted attention from the azo compound.

LXIII



"Scarlet red"

LXIV



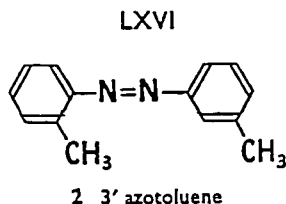
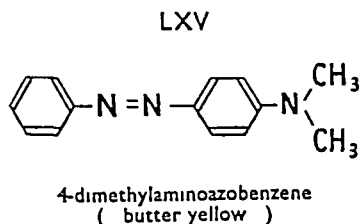
4'-amino-2 3'-azotoluene

⁵ [See also BMB 973—Ed.]

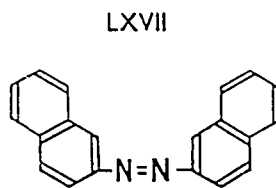
⁶ [BMB 974]

In 1924 Schmidt, during a study of "Sudan" dyes in vital staining noted that feeding of scarlet red produced epithelial proliferation (adenoma) in the liver of mice. This observation remained largely neglected, and little progress was made before 1931, when Yoshida (1934) observed the production by means of 4'-amino-2,3'-azotoluene of liver-tissue proliferation in mice. Varying his technique, Yoshida was able to report liver tumours in rats which had been given the same compound over long periods in the diet.

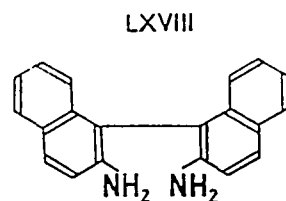
Kinosita (1940) later examined many other derivatives of azobenzene, and found an isomer of aminoazotoluene—4-dimethylaminoazobenzene (LXV)—to be highly active in producing liver tumours. This substance, with 4'-amino-2,3'-azotoluene and 2,3'-azotoluene (LXVI), is also capable of producing connective tissue growths. Yoshida also noted in a few of his animals, papilloma-formation in the stomach and bladder, and bladder tumours were later obtained with 2,3'-azotoluene. Recently Kirby (1944) has examined the carcinogenic effect of 4-aminoazobenzene itself.



In other attempts to produce bladder cancer, Cook, Hewett, Kennaway & Kennaway (1940) selected the three azonaphthalenes, on the supposition that these might arise by oxidation of mixtures of naphthylamines and so be present in the crude bases, exposure to which is a factor in the occupational incidence of the disease in chemical workers. No tumours of the bladder were obtained, but liver changes in mice, similar to those induced by the azobenzene derivatives resulted from treatment with 2,2'-azonaphthalene (LXVII). Since azo compounds may be reduced in the body to amines by way of the hydrazo compound and since this is susceptible to rearrangement, Cook and his colleagues (Cook *et al.*, 1940) then made tests with the compound which might thus be expected viz 2,2'-diamino-1,1'-dinaphthyl (LXVIII). This induced liver tumours with even greater facility than 2,2'-azonaphthalene, a finding of interest since the diaminodinaphthyl readily undergoes deamination to 3,4,5,6-dibenzcarbazole (LVII) which as previously stated itself produces liver tumours as well as skin cancer and malignant connective tissue tumours in mice.



2,2'-azonaphthalene



2,2'-diamino-1,1'-dinaphthyl

8 Derivatives of 4-Aminostilbene

An entirely new class of carcinogenic substances has recently been discovered, by means of an approach quite different in character from any so far considered (Haddow, Harris & Kon, 1945). In an investigation of the mode of action of carcinogens, one of the writers described a growth-retarding or inhibitory effect possessed by many of the polycyclic aromatic hydrocarbons, the nature and possible significance of which will be further discussed in a following article⁷ (Haddow, 1947). Suffice it to say here that evidence of very different kinds has meantime been collected which supports a causal connection between these two biological properties of carcinogenicity and growth-inhibitory power.

During earlier experiments several instances were encountered in which the inhibitory property was detected in hydrocarbons then believed to be non-carcinogenic on the basis of a given experiment. In a few such cases (of which 3-methyl-1,2-benzanthracene was a striking one) subsequent re-test showed the compound to be in fact carcinogenic and sometimes markedly so, especially when administered by the subcutaneous route in preference to application to the skin. Although cases of this kind could in no sense be a proof of the suspected relationship (which was, however, highly probable from a statistical analysis of all the results accumulated), they did allow a certain degree of confidence. Later experiments covering a wide variety of chemical classes such as the polycyclic hydrocarbons, many heterocyclic analogues, azo compounds, synthetic oestrogens and others, revealed interesting examples of variation in inhibitory power which again could often, although not always, be related with carcinogenicity or its absence.

In due course attention became directed to 4-dimethylaminostilbene (LXIX, R = CH₃), when it was at once apparent that this type exhibited the seemingly characteristic inhibitory property to a high degree (on average, approximately tenfold that shown by the carcinogenic hydrocarbons). Notwithstanding the fact that this compound and even more 4-aminostilbene (LXIX, R = H) are highly toxic, examination of other compounds (e.g. LXX) showed that certain features at any rate of this toxicity were not essential for the production of the growth-retarding effect. Since many compounds of the series, of which LXXI is another example, showed this biological property *par excellence*, steps were at once taken to test whether these compounds too were endowed with carcinogenic properties. It soon became apparent that this was in fact the case and not merely so, but that their carcinogenicity had features

⁷ B.M.B. 9641

of a novel kind. For compounds LXIX, LXX and LXXI, with acetaminostilbene in addition, carcinogenicity has been demonstrated in the albino rat, in all cases by subcutaneous injection, and for 4-dimethylaminostilbene also by incorporation in the diet. Sarcomata have also been produced in mice by subcutaneous injection of both 4-amino and 4-dimethylaminostilbene, but the yield of tumours is small, and it appears that the carcinogenicity of these compounds for the mouse is probably considerably lower than for the rat. This species-difference is specially interesting, since it appears also to apply to the inhibitory effect, the latter being much more striking in the rat. Tumour-production in the rat was characterized by a relatively long latent period (6-12 months or more), and by a substantial yield of tumours both at the site of injection and at a distance of the compounds tested, the greatest activity so far is shown by LXXI.

The tumours produced by these compounds in the rat include sarcomata at the point of injection, basal-celled

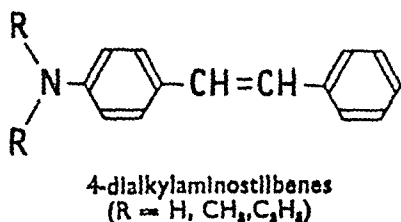
aminofluorene, and it is particularly striking, as Bielschowsky (1946), too, has remarked, that squamous keratinizing carcinomata of the acoustic duct should be produced by 2-acetylaminofluorene, 2-aminoanthracene and derivatives of 4-aminostilbene, since this species of tumour had not been previously described. Of course, there are certain differences in detail between the carcinogenicity of 2-acetylaminofluorene and that of the aminostilbenes—witness the facility with which sarcomata are produced by the latter, and the relatively benign character of the mammary tumours induced with aminostilbenes. But the general biological similarity is undoubtedly striking, and may reflect a certain degree of chemical affinity between 2-aminofluorene and 4-aminostilbene, which will be referred to elsewhere.

A useful feature of the aminostilbene series is the relative facility with which a programme can be designed to decipher the relationships between chemical constitution and biological action. Of course, there must still remain the necessarily lengthy process of direct test for carcinogenicity, but so far as the inhibitory effect alone is concerned, activity would appear to depend essentially upon a basic group in the *p* or *o* position, an ethylene bridge (and not one of three or more carbon atoms) in which neither hydrogen atom must be substituted, a free *p'* position, and the *trans* configuration of the molecule as a whole.

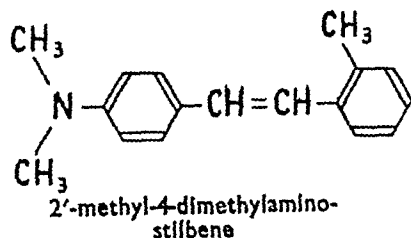
In an extension of the above lead, which is being carried out by Mr D. M. Brown, interesting cases are being discovered in which ring B can be replaced by various heterocycles, while still retaining growth-inhibitory capacity. One such type is represented by 2-(4-dimethylamino)-styrylquinoline (LXXII), which, again, shows inhibitory properties which suggest that it should be tested for carcinogenicity. This compound is of special interest since, if the test proves positive, the question will be raised whether the carcinogenic activity of the trypanocide styryl-430 (LXXIII), originally described by Browning, Gulbransen & Niven (1936), may be connected with the styrylquinoline fragment which this compound contains in its structure.

Although the range and diversity of carcinogenic compounds is nowadays such as might throw doubt on the likelihood of any underlying chemical specificity of their action, such possibilities, and other examples already quoted

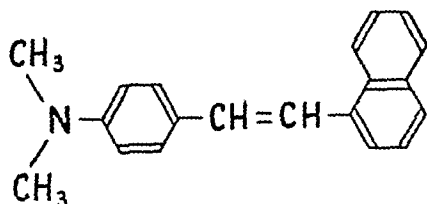
LXIX



LXX



LXXI

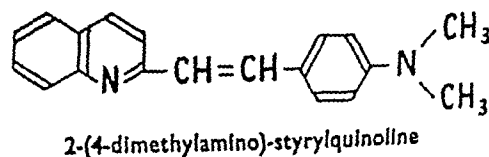


α-(4-dimethylaminophenyl)-β-(α-naphthyl)-ethylene

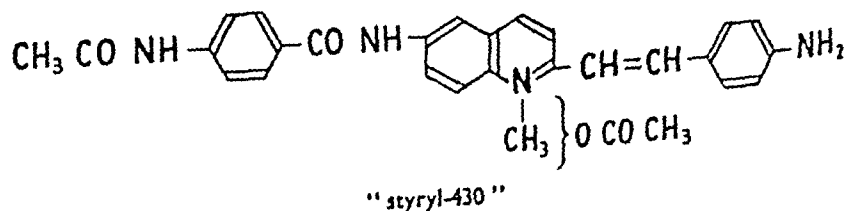
carcinomata, carcinoma of the eye-lid, squamous-celled carcinoma, particularly arising from the epithelium of the external acoustic duct on one or both sides, but also occurring on the face and in other regions, distant and multiple subcutaneous fibromata, cholangiomata of the liver, multiple mammary fibro-adenomata in females (in many cases accompanied by cholangiomatous and other changes in the liver), adenomata of the lung, and a few examples of intestinal carcinoma and hypernephroma.

The nature of these tumours, and their distribution, is somewhat reminiscent of the variety of neoplasms produced by 2-acetyl-

LXXII



LXXIII



in the cyclic hydrocarbons, azo compounds and carbazoles show that there may after all be not merely a community of structure between active compounds of a given class, but that remarkable linkages between one class and another may also be found. Such linkages between the carcinogenic azo-compounds and carbazoles, between aminoanthracene, aminofluorene and the aminostilbenes, and possibly between aminostilbenes and such an apparently exceptional compound as styryl-430, offer the prospect of eventually establishing a more comprehensive and meaningful relation between molecular features and biological action.

9. Miscellaneous Substances, Radioactive Elements, Arsenic, Urethane

While the above survey is probably sufficient for the main purpose of the present symposium, it by no means completes the list of carcinogenic agents. Since cancer attributable to arsenic is separately considered by Dr Currie elsewhere⁹, no further reference will be made to it here. Perhaps the most important remaining class is the radioactive elements, and a voluminous literature now testifies to the exceptional production of tumours by the salts of radium, thorium, mesothorium and by radon. The potential carcinogenic action of radioactive paints has long been recognized as an important industrial risk from the work of Martland (1931) and of Martland & Humphries (1929), and it is clear that modern developments in atomic physics, in rendering available radioactive isotopes in increasing variety and abundance, must greatly add to the scientific and practical problems which the potential carcinogenicity of such substances creates.

A progress report has just appeared (Brues, Lisco & Finkel, 1947) on the late effects in different animal species of exposure to plutonium and various radioactive products of uranium fission. Radioactive strontium (Sr^{90}), with a 55-day half-life, has a marked tendency to concentrate in the skeleton and to produce tumours of bone in mice. Bone sarcomata are also produced by radioactive cerium-presyodimium ($\text{Ce}^{144}\text{-Pr}^{144}$) and by plutonium (Pu^{239}). Following subcutaneous administration of 1 μg . of the last element, fibrosarcomata also appear at the site of injection. The carcinogenic effect in rats and mice of high-energy radiations associated with the uranium chain reaction are also described by Henshaw, Riley & Stapleton (1947). With penetrating radiations, the main terminal effects are generalized atrophy and the appearance of neoplasms of the haemopoietic tissues and mediastinal

lymphomatosis. When non-penetrating radiations were used, the changes were limited mainly to the skin. Several months after single massive doses, in animals which rarely showed spontaneous skin lesions of any type, the incidence of carcinoma was raised to 100% and the number of tumours per animal was as great as 50-100.

Among recently-discovered carcinogens of a different kind, special interest attaches to urethane, which was shown by Nettleship & Henshaw (1943) to have the power of greatly increasing the incidence of lung adenomata in mice. This observation has now been completely substantiated by others. In particular, Jaffe (1944) found that all animals, in a strain not showing lung tumours spontaneously, had developed such tumours after 157 days from the first of 15 injections of a 10% urethane solution, or after 119 days on a diet containing 0.2% of urethane. These experiments further showed the high specificity of urethane upon the lung tissue of mice, since methylcholanthrene, in the same stock, produced an incidence of pulmonary adenomata of only 8%. More recently, Larsen & Heston (1945) have brought forward evidence of the chemical specificity of the effect, since it is essentially confined to urethane itself (ethyl carbamate), is not shown to any extent by other alkyl carbamates, is considerably modified by substitution of either or both of the amino hydrogen atoms of ethyl carbamate and is absent in the case of a considerable number of barbituric-acid derivatives and other narcotics.

* * * * *

Enough has been said to indicate the history of experimental carcinogenesis, the great number and variety of pure compounds now known to possess carcinogenic properties and the fascinating relationships often seen to exist between one class and another. While the list is almost certainly incomplete, the discovery of fresh examples will be valued in future not only for their own sake, but increasingly in proportion as they facilitate a more complete synthesis of all our available knowledge. From the days when the deliberate induction of cancer was a novelty, even when achieved with as crude a mixture as coal-tar, or pitch, the whole subject has been steadily active and growing, although with many a change of emphasis. It now enters upon an entirely new phase, in which attention is tending progressively to concentrate upon problems of mode of action that is the intimate details of the manner in which the carcinogen converts the normal cell into a malignant one. This different aspect is treated separately below⁹.

⁹ [BMB 977]

⁹ [BMB 964]

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SOME PHYSICAL METHODS OF INVESTIGATING CARCINOGENIC HYDROCARBONS

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Rapid advances in chemical and biological sciences are often made possible by timely discoveries of appropriate physical methods. An example of this is seen in the field of carcinogenesis connected with polycyclic hydrocarbons. The following is a short account of the scope (and limitations) of the methods that have proved most valuable, with brief mention of certain others of more recent and less extensive use, which may possibly find wider application in the future.

1. Naked-eye and Microscopical Examination of Fluorescence

Most aromatic polycyclic hydrocarbons, and many of their derivatives, fluoresce in ultra-violet light, and can thus be detected, often in very small amounts, by such illumination. Advantage has been taken of this in chromatography (see below), and also in a variety of biological studies (see Peacock, 1940, 1944). Naked-eye and microscopical examination of animal tissues in ultra-violet radiation has played an important part in such studies as (i) the distribution of carcinogens in various parts of the body after injection (Peacock, 1936, 1940, Doniach, Mottram & Weigert, 1943a, b), (ii) their persistence in the skin after application (Hieger, 1936, Simpson & Cramer, 1943, 1945), (iii) as a preliminary indication of their manner of metabolic conversion and elimination *in vivo* (Peacock, 1936, and others, see review by Boyland & Weigert, in this number), and (iv) as a histochemical procedure (Graffi, 1939). Spectrographic analysis of the emitted fluorescence has, however, provided more precise information, and calls for fuller discussion.

2. Fluorescence Spectrography

The introduction of the spectrographic study of fluorescent light (Mayneord, 1927), as a method of investigating complex mixtures of hydrocarbons in tar, served as an essential step in the work which led to the isolation and identification of

* [See BMB 968—ED]

CHEMISTRY OF CARCINOGENIC COMPOUNDS

Continued from page 325

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benzpyrene as a cancer-producing constituent of pitch (Hieger, 1930, 1937, Cook, Hewitt & Hieger, 1933)

Working on the problem of carcinogenic tars and oils, Hieger (1930) investigated the fluorescence spectra of a wide range of hydrocarbons and related compounds, and found many of the polycyclic members to possess banded spectra, some of which appeared sufficiently distinctive (in pattern and positions of the bands) to characterize them with some confidence (This property proved especially valuable in the isolation of 3,4-benzpyrene.) In some cases, however, dissimilar compounds (or different derivatives of the same compound) appeared to possess identical spectra. This low specificity was due in part to the use of a spectrograph of low dispersion, but depended more on the fact that the individual bands were few in number and not always sharp.

In recent studies (Berenblum & Schoental, 1946), some of the difficulties have been overcome by the use of a spectrograph of larger dispersion, and more especially by the interposition of a "moving wedge" near the slit, thereby converting the wide bands into peaks (see Fig 1). In comparing the spectra of different polycyclic hydrocarbons, isomeric substitution products, and related compounds, they were able to show a considerable degree of specificity (e.g. sufficient to differentiate the six isomeric methoxychrysenes), though confirming Hieger's main thesis that identity of fluorescence spectrum does not always denote proof of identity in structure.

The advantages of fluorescence spectrography are that (i) the procedure is simple once the apparatus is set up, (ii) the method is highly sensitive requiring very small amounts of material (e.g. the benzpyrene bands are detectable in a concentration of 1/20,000,000 or less, though higher concentrations are needed for most other compounds), (iii) tests can often be carried out in the presence of impurities (provided that these are not highly coloured, or, if themselves fluorescent, provided that the bands are in different positions), and (iv) the method can be adapted for quantitative estimations (see below). A modification which provides fluorescence spectra of substances adsorbed on alumina columns or contained in tissues (Doniach *et al.*, 1943a) gives promise of further useful application.

The limitations of fluorescence spectrography are that (i) the method is restricted to the class of fluorescent substances that display banded spectra, (ii) the specificity is, as already stated, only relative so that while spectral differences are proof of non-identity of compounds similarities of spectra though indicative of structural identity, cannot always be interpreted as proof of it, and (iii) the results obtained are influenced by many factors, including the nature of the optical system, the sensitivity of the plates, the solvent, the light source etc., so that comparisons are valid only under given conditions. (For fuller discussions, see Miller & Baumann 1943, and Weil-Malherbe 1944, on quenching of fluorescence, Berenblum & Schoental 1946, on the use of fluorescence spectrography for identifying compounds, and Bowen, 1946 on theoretical aspects of fluorescence.)

3 Absorption Spectra

Observations of spectral absorption of aromatic polycyclic hydrocarbons and their derivatives have also considerably aided the study of carcinogens particularly of their distribution between the various body-tissues (Jones 1942) and their metabolism (Boyland, Levi, Mawson & Roe 1941,

Dobriner, Rhoads & Lavin 1939, 1942, Berenblum, Crowfoot, Holiday & Schoental 1943, Berenblum, Schoental & Holiday, 1943, Berenblum, Schoental, Holiday & Jope 1946). The dosage of hydrocarbon required to initiate a tumour is often, however, far lower than that used in these metabolic experiments, and it remains uncertain whether the fraction of the hydrocarbon which is instrumental in carcinogenesis follows the same metabolic path as the bulk of material. The minimal doses for carcinogenesis are probably too low for standard spectroscopic techniques to be applicable (but see section 7 of this review).

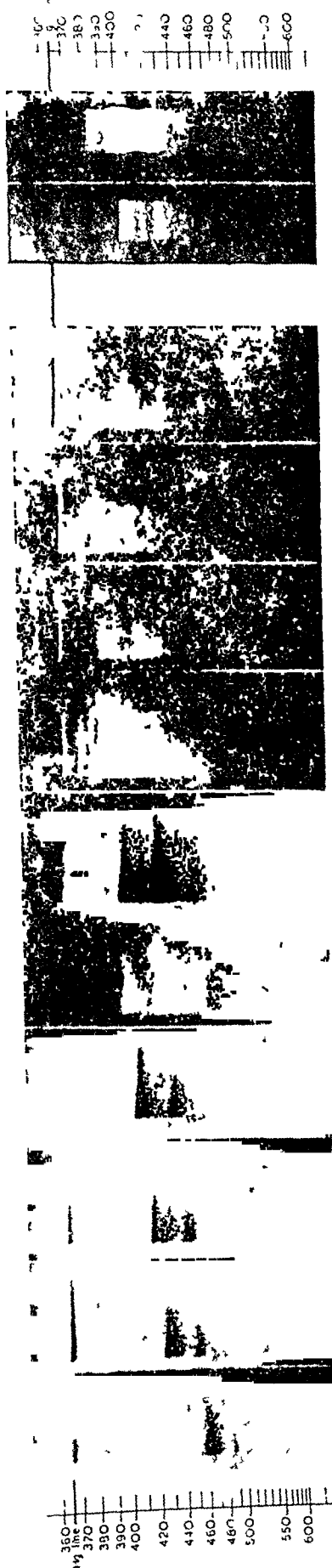
The ultra-violet absorption spectra of these compounds are very intense and exhibit elaborate patterns of fine structure by means of which they can be identified even in small amounts. These patterns depend upon the molecular vibrations, and isomeric compounds, derived from a given conjugated double-bond system with one substituent in different positions, show easily distinguishable spectra, though the general character is in each case recognizably that of the double-bond system. Thus, Fig 2 and 3 show spectra of 3,4-benzpyrene and of its 5-, 8-, and 10-methoxy derivatives.

The usual spectral absorption curves are chiefly of use for quantitative studies (Chalmers, 1934, Jones, 1942, see below), which can be carried out on 0.5 µg or less of these hydrocarbons. For the identification of these compounds however, the wavelengths of the fine-structure peaks must be measured accurately, and a technique has been devised (Holiday, 1937a, 1945) for obtaining these more satisfactorily than from absorption curves. The spectrograms in Fig 2 were obtained by this technique and may be compared with the curves for the same compounds (Fig 3). Examination by this technique may be carried out on even less than 0.1 µg of many of these hydrocarbons, and it may be used to give information about such compounds with fine structure in their spectra even in very impure extracts (Holiday, 1937b), which is useful in biological work. It is rapid, semi-quantitative, and need not require very elaborate equipment.

Identification of these compounds from their absorption spectra is still largely a matter of comparison with the spectra of those whose structures are known from synthesis or other chemical arguments. Mayneord & Roe (1935, 1937) started a systematic collection of spectral data from model compounds, and subsequent work has been summarized by Jones (1943), but so many new compounds of interest in this field are being made that the work expands faster than it can be covered. Certain conclusions as to structure may sometimes be derived from more theoretical arguments. Thus the structure of a partially hydrogenated dibenzanthracene (I) may be deduced from the resemblance of its spectrum to the naphthalene type, eliminating the benzanthracene (II) or phenanthrene-plus-benzene (III) structures (Mayneord & Roe, 1935, 1937, see also Kon & Roe 1945). Anomalies are however sometimes encountered in these cases (e.g. Morton & de Gouveia 1934), and comparisons with known structures are desirable whenever possible. Such hydrogenated derivatives may occur among hydrocarbon metabolites (Berenblum *et al.* 1946).

The scope and limitations of fluorescence and absorption spectra may be compared. Absorption spectra are in general more specific than fluorescence spectra and are considerably less influenced by the experimental conditions. With these compounds the sensitivity of absorption spectra observa-

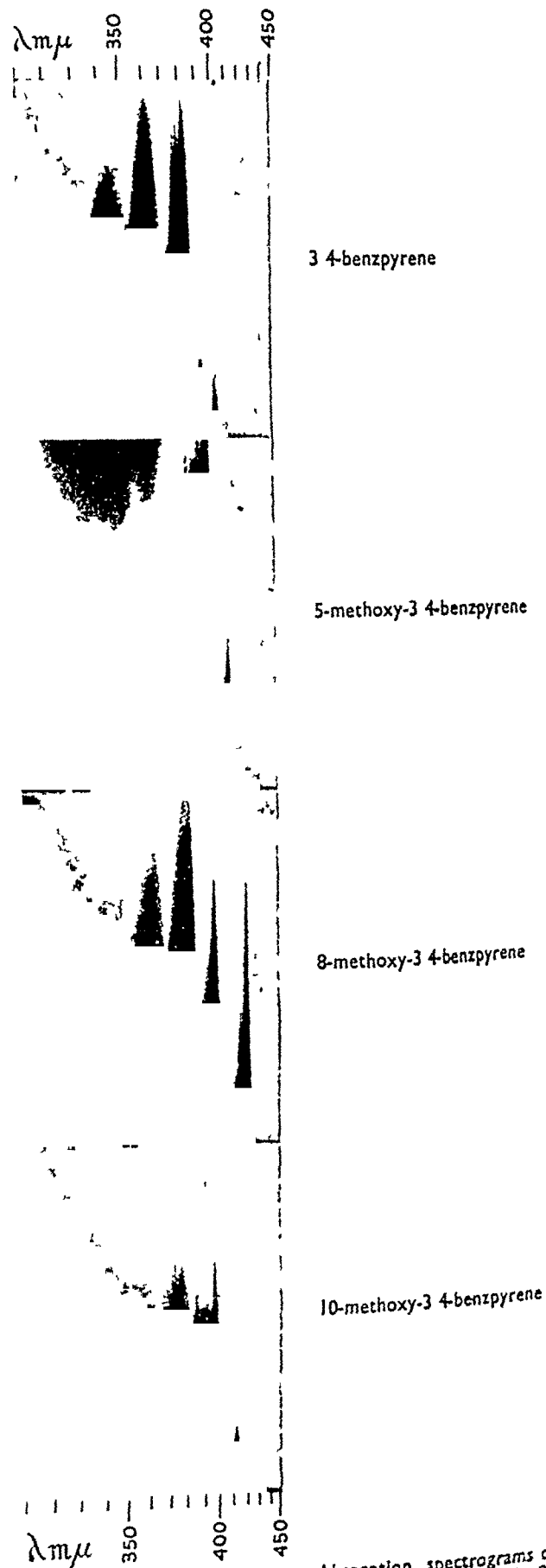
FIG 1. FLUORESCENCE SPECTRA
OF HYDROCARBONS



- 1 anthracene
- 2 3 4-benzpyrene
- 3 anthracene
- 4 chrysene
- 5 1 2-benzanthracene
- 6 pyrene
- 7 1 2 5 6-dibenzanthracene
- 8 20-methylcholanthrene
- 9 3 4-benzpyrene
- 10 10-methoxy-3 4-benzpyrene
- 11 8-methoxy-3 4-benzpyrene
- 12 3 4 8 9-dibenzpyrene

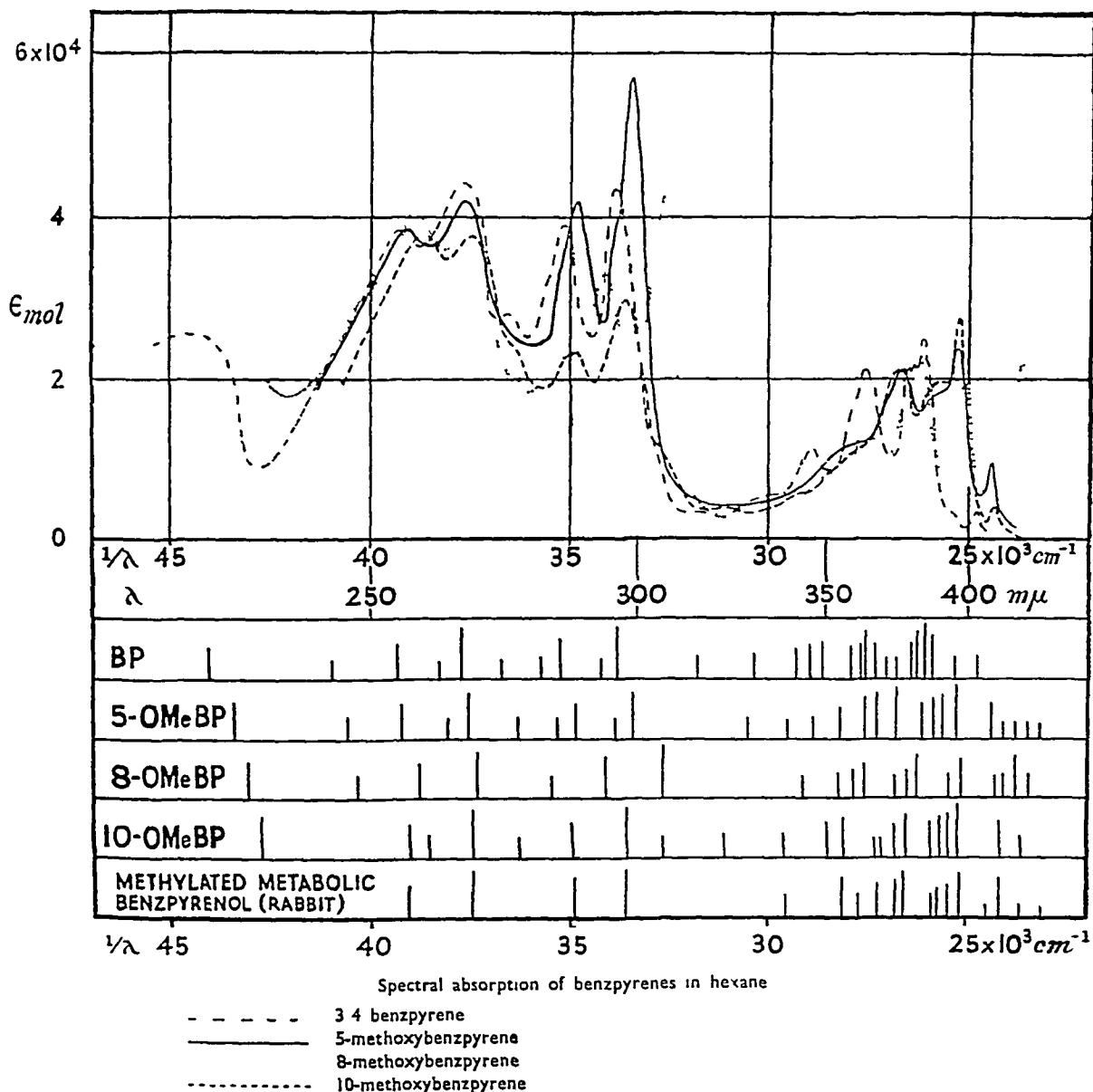
Spectra 1 and 2 are by simple exposure, the remainder by the "moving wedge" method. All tested in solution in liquid paraffin

FIG 2. ABSORPTION SPECTROGRAMS



Absorption spectrograms of 3 4 benzpyrene and of its 5-, 8-, and 10-methoxy-derivatives, in hexane to illustrate the detailed fine structure

FIG 3 SPECTRAL ABSORPTION

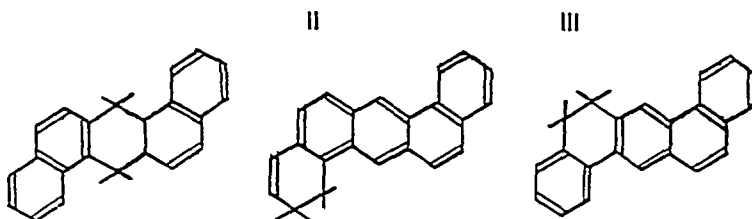


The fine structure bands indicated diagrammatically have been taken from spectrograms as shown in Fig 2

tions is of the same order as that with fluorescence spectra. In any case, the two methods are complementary, evidence from both being much more conclusive than that from either alone.

4 Polarography, Crystallography, etc.

Polarography may be useful in the study of some carcinogens (Waterman, 1937, 1939, Wawzonek & Laitinen 1942) being sometimes applicable to 1 μg of compound.



Crystallographic and x-ray examination have also proved useful in the identification of hydrocarbon metabolites (Chalmers & Crowfoot, 1941, Berenblum *et al.*, 1943)

5 Chromatography

Though chromatography is nowadays accepted as a standard technique in most chemical laboratories, its application to polycyclic hydrocarbons is of special interest, first, because much of the existing knowledge about the relation of chemical structure to chromatographic behaviour was elucidated by the study of these compounds (Winterstein & Schon, 1934, Winterstein, Schon & Vetter, 1934, Winterstein & Vetter, 1934), and second, because of the important rôle chromatography has played in the isolation of metabolites of polycyclic hydrocarbons (Chalmers, 1940, Dobriner *et al.*, 1942, Berenblum & Schoental, 1943a, Berenblum, Schoental & Holiday, 1943, Berenblum *et al.*, 1946, Weigert & Mottram, 1943, 1946, etc., see also review by Boyland & Weigert in this number)

The use of chromatography for fractionating tars and oils has led to the unexpected detection of benzpyrene in shale oil, as well as to the separation of carcinogenic, benzpyrene-free fractions (Berenblum & Schoental, 1943b), and also of highly carcinogenic, benzpyrene-free fractions from coal tar (British Empire Cancer Campaign, 1943)

6 Quantitative Estimations of Hydrocarbons

The quantitative estimation of benzpyrene, and of other hydrocarbons, in biological materials (at various periods after injection of these compounds into the animal body) is based on one of two methods (i) by fluorescence spectrography (by matching the intensities of the bands with those of standard solutions) or fluorimetry, and (ii) by absorption spectrography (by extinction coefficients). With some tissues, simple extraction of the desiccated material with benzene, etc., is adequate, but with more complex materials (e.g. faeces), or with whole carcasses, preliminary chemical disintegration of the tissue, and elaborate methods of purification of the extracts, are necessary. The former is usually achieved by boiling with alcoholic potash, while the latter (involving chromatography and other procedures) varies according to the degree and kind of purification required, i.e. whether for estimation by fluorescence spectrography (Berenblum & Kendal, 1936, Berenblum & Schoental, 1942), absorption spectrography (Lorenz & Shear, 1936, Dobriner *et al.*, 1942, Jones, 1942), or fluorimetry (Weil-Malherbe, 1944). (For separation and estimation of intermediate products of metabolism of benzpyrene, see Weigert & Mottram, 1946)

7 Aqueous Dispersion of Carcinogenic Hydrocarbons

Aromatic polycyclic hydrocarbons are soluble in organic solvents and oils but insoluble in water. Hence, solutions in benzene or acetone are usually used for skin painting and

solutions in oils for subcutaneous injection. Certain investigations (e.g. those involving intravenous injections) cannot be carried out in such media, and attempts have, therefore, been made to circumvent the limitation of insolubility in water.

The preparations used include colloidal suspensions in water or aqueous gelatin (Boyland, 1932, Berenblum, 1932), aqueous solutions of complexes with bile acids (Winterstein & Vetter, 1934), suspensions in serum (Lorenz & Andervont, 1936), purines (Druckrey, 1938), glycerin (Graffi, 1939), olive-oil water emulsions (Lorenz & Stewart, 1940), and aqueous solutions of soap (Beck, 1943). None of these is ideal for all purposes, since the concentrations obtained are low, the suspended particles are coarse (and tend to form even coarser aggregates in the blood-stream, resulting in their accumulation in the lung capillaries, cf. Peacock, 1940), and some, at least, of the preparations are toxic. To overcome the difficulties, water soluble derivatives have been synthesized (Cook, 1931, Fieser, Fieser, Hershberg, Newmann, Seligman & Shear, 1937, etc.), but these, too, have serious limitations, since the stable derivatives have entirely new biological properties while the unstable ones revert quickly in the body into the (water-insoluble) parent hydrocarbon.

Stamer (1945) used aqueous suspensions by addition of poly-ethylene oxide types of compounds (e.g. "Postonal," Danigefa Ltd, Copenhagen). This procedure may prove to be the solution of this vexed problem, since high concentrations can be obtained, providing very fine emulsions (which are not trapped in the lung capillaries).

8 Future Developments

An important possible development is the seeking of carcinogens in individual cells of tumour or other tissue by methods of spectromicrography similar to those developed by Caspersson (1940) and others. No such work has yet been reported. As the necessary equipment is elaborate, it is as well to know beforehand the probable limitations of the data obtainable. Taking a spherical tissue cell of 10μ diam. $10^6 \mu g$ of benzpyrene evenly distributed through its cytoplasm would show an extinction coefficient of about 0.1 for the peaks in the wavelength range 300-400 $m\mu$, where other cell constituents absorb little. Such absorption should be detectable, and, by a modification of Holiday's (1937a) technique, using a powerful hydrogen arc as a continuous source, the fine structure patterns might be identifiable.

But such concentrations of hydrocarbons, corresponding to $2 \mu g$ per mg of tissue, represent a high degree of localization of carcinogen, bearing in mind the small amounts required to initiate a tumour. The significant carcinogen molecules might well not be homogeneously distributed through the cytoplasm, but spectromicrography might reveal local concentrations within the cell structure of $10^7 \mu g$ of some carcinogens. Similar arguments may be applied to the possibility of obtaining useful results from fluorescence spectromicrography.

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Continued at foot of page 331

MODE OF ACTION OF CHEMICAL CARCINOGENS

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- 1 Physical properties
 - 2 Chemical relationships
 - 3 Substitution and addition reactions
 - 4 Energy states in the carcinogenic molecule
 - 5 Biological considerations
 - 6 Carcinogenesis and cellular nutrition
 - 7 Energetics of the malignant transformation
 - 8 Relation to the viruses of chicken sarcoma
- References

Sufficient has already been said in a previous paper¹ (Haddow & Kon, 1947) to indicate the nature, number and great variety of the chemical carcinogens. Several hundreds of these are at present known and while the list is almost certainly far from complete it is natural that less attention should now be paid to descriptions of the carcinogens alone and progressively more to their mode of action.

¹ (BrMB 962)

Hence, the problems of major importance which must now concern us are rather the nature of the structural relationship between carcinogens of one chemical class and those of another, the extent to which any such community of structure may signify a common principle of action, and finally, the nature of that action itself by which the biological change, from the normal to the malignant state, is achieved. Before proceeding it may be noted how comparatively little in the way of correlation has been obtained, at least until very recently, by the use of purely physical methods, how fertile in contrast have been the suggestions arising from the chemical and biochemical attack, and how consonant these are with independent evidence from an exclusively physiological or biological approach, which has in itself been able to establish a practical working hypothesis comprehensive enough to include carcinogens of the most varied types and apparently sound enough to predict the activity of an entirely new class—the aminostilbenes.

1 Physical Properties

So far as physical properties are concerned the great majority of all chemical carcinogens are virtually insoluble in water, although soluble in lipoids and to some extent in body-fluids such as serum and bile, but no relation exists directly at any rate between the greatly varying degrees of such solubility and carcinogenic action. For the polycyclic hydrocarbons no specific differences have been disclosed.

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Continued from page 330

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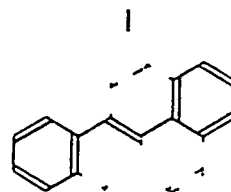
between carcinogens and non-carcinogens, by means of either fluorescence or ultra-violet absorption spectroscopy. In the case of the aminostilbenes, the ultra-violet absorption spectra of a considerable series are being investigated by Dr. E. M. F. Roe, and will be reported upon later. For both the carcinogenic hydrocarbons and aminostilbenes, it is too early to say whether developments may arise from the radically different type of information to be obtained by the application of infra-red spectroscopy. Other physical or physico-chemical techniques, such as the interaction of carcinogens with monomolecular films of sterols, proteins and other substances, have still been very inadequately studied, although Clowes and his collaborators (Clowes, 1943) suggested that this type of interaction might influence the normal function of cholesterol.

2. Chemical Relationships¹

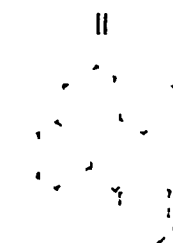
The possibility has already been discussed in a previous paper (Haddow & Kon, 1947) that certain azo compounds, exemplified say by 2,2'-azonaphthalene, may be re-arranged and transformed into carbazoles in the liver (in this case into 3,4,5,6-dibenzcarbazole) and there produce tumours of that organ. Although no proof has so far been obtained that such a process is effected *in vivo*, it seems a legitimate question whether such chemical transformations, even if they do not represent the mechanism itself, should be regarded as significant and important affinities if only in the theoretical sense. In the case of 4-aminostilbene, which produces tumours in the rat of a type and distribution similar to those produced by 2-acetylaminofluorene, a similar suggestion was made to the writer by Dr. F. L. Rose, of a conversion to 3-aminofluorene or to 2-aminoanthracene. Here again, even if such a mechanism is regarded as an extremely unlikely explanation of the action of 4-aminostilbene in the body, its chemical feasibility has perhaps some underlying meaning which we should not ignore.

Whatever may be the ultimate prospect of deriving logical relationships between them, it still remains a fact that compounds of widely different features in the purely chemical sense (as anthracenes and fluorenes, aminostilbenes, acridines and carbazoles) may none the less show an important biological property in common. Some of these cases led Cook (Barry, Cook, Haslewood, Hewett, Hieger & Kennaway, 1935) to indicate the significance, in themselves, of general molecular shape and dimensions, and a somewhat similar opinion was held by F. Bergmann (1942), who conceived the molecule as functioning as a whole, and its activity as being determined by shape and size. Bergmann suggested that all the carcinogenic hydrocarbons might be absorbed by a single receptor, and that all such compounds might be regarded as parts of an "ideal" carcinogenic structure. According to this view, geometrical conformity of carcinogen and receptor is a necessary condition for activity, although not a sufficient one. Pursuing these notions, it is a logical step to consider if the wide range of compounds already examined, or some class among them, possesses any structural characters in common, such as might indicate the essential nature of the carcinogen-receptor relation. It may be said at once that this is almost certainly not so, but the writer has been impressed by a curious relation in certain pairs of isomers, one of which is carcinogenic and the other inactive or only feebly active, and according to which the active molecule alone might appear to incorporate

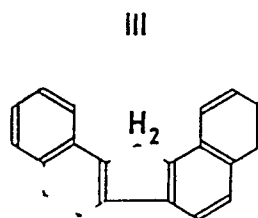
the skeletal structure of a *trans*-diaryl "ethylene", two such pairs are shown (I-IV) contrasting the carcinogens 3,4-benzpyrene and 1,2,7,8-dibenzfluorene with the inactive or feebly active 1,2-benzpyrene and the non-carcinogenic 3,4,5,6-dibenzfluorene.



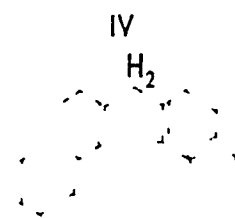
3,4-benzpyrene



1,2-benzpyrene

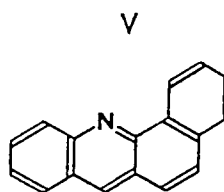


1,2,7,8-dibenzfluorene

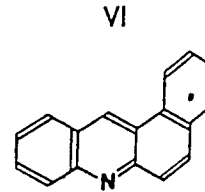


3,4,5,6-dibenzfluorene

If such a relation were to represent more than mere coincidence—and Pacault (1946) has adduced evidence for the existence of "ethylenic" structures in such aromatic nuclei—one might anticipate a marked distinction in carcinogenicity between the homologues of 1,2-benzacridine (V), which could not incorporate the *trans*-diaryl "ethylene", and of 3,4-benzacridine (VI), it is of interest that Lacassagne and his colleagues (Lacassagne, Rudali, Buu-Hoi & Lecocq, 1945; Lacassagne, 1946) have, in fact, described a strong contrast in carcinogenicity between the two series, but in the opposite sense to the above¹. In many other examples, too, e.g. the carcinogenic alkyl substituted 3,4-benzphenanthrenes, it is clear that no such simple relation could possibly hold.



1,2-benzacridine



3,4-benzacridine

Notwithstanding the absence of any very obvious clue, the extent of the existing data on effects of alkyl and other substitution in 1,2-benzanthracene alone, makes it very desirable that these data should soon be re-examined in a further attempt to generalize the relation between chemical constitution and carcinogenic action. Some time ago the writer obtained, with the help of Dr. H. O. Hartley, partial evidence that the carcinogenic derivatives of benzantracene may be members of a series, so far as their geometry alone is concerned. The matter still requires very much closer scrutiny, and one would therefore hesitate to advance even the most

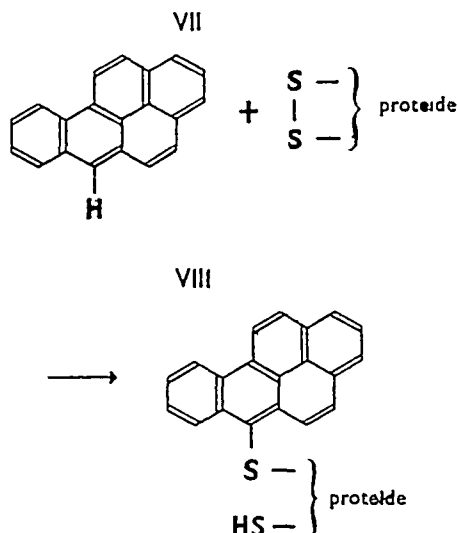
tentative hypothesis But it appears to be not beyond the bounds of possibility to derive in the future, by purely numerical or geometric methods, an expression which would generalize all the information we already have in so many individual cases concerning the effects of substitution on the carcinogenic activity of this group at least Such an expression would clearly represent simply a comprehensive statement, in the smallest number of terms, of what we already know, but one gathers, assuming it could be fully verified, that it might also indicate some relationship not so apparent from the individual data themselves, and that it might reflect, without giving any direct indication of its nature, some type of reactivity necessary for this kind of biological action

3 Substitution and Addition Reactions

Although as a class the carcinogenic hydrocarbons must be regarded as comparatively inert, they are nevertheless susceptible to oxidation eventually yielding non-carcinogenic quinones Since anthracene is known to inhibit the auto-oxidation of benzaldehyde, it has been suggested that the activity of the carcinogenic hydrocarbons may be due to some similar inhibition of the normal oxidative processes of the cell Fieser (1941) laid great stress on the fact that the most potent of the carcinogens are endowed with a remarkable susceptibility to substitution reactions, and surpass all other known aromatic hydrocarbons in this type of reactivity Studying this phenomenon with the reactions of diazo coupling, lead tetra-acetate oxidation oxidation with perbenzoic acid, and condensation of the hydrocarbons with sulphur monochloride, he found in general that the order of reactivity was essentially the same for a given group of compounds, and declined in the following sequence methylcholanthrene > 3 4-benzpyrene > 10-methyl-1 2-benzanthracene > 1 2 5 6-dibenzanthracene Again as for every correlation yet attempted there are exceptions, especially in the case of certain anthracenes equally susceptible to oxidation but these did not appear to Fieser to invalidate the notion of a causal association between chemical reactivity and carcinogenesis, provided that other essential requirements such as solubility, absorbability and molecular size were also satisfied by a given compound

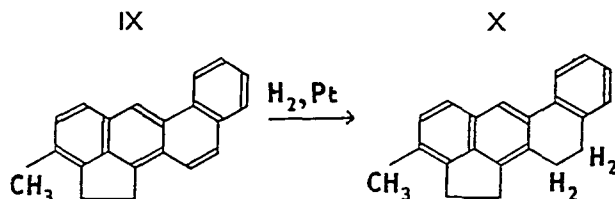
Such considerations suggested that the carcinogenic molecule undergoes a substitution reaction as the first stage in the production of its biological effects The earliest possibility to be considered was introduction of a hydroxyl sulphhydryl or basic group leading to a functional derivative which might then enter into other changes possibly involving conjugation with constituents of the cell Later, a more direct interaction was suggested by the condensation of sulphur monochloride with carcinogenic hydrocarbons, with the most potent and reactive hydrocarbons, introduction of a sulphur substituent occurs at room-temperature without catalyst and Fieser suggested that possibly the carcinogen similarly combines with cell proteins by the opening of an S-S linkage as indicated for 3 4-benzpyrene in VII and VIII

So far as addition reactions are concerned Fieser indicated that the carcinogens enter into such reactions only sluggishly, and are attacked at points *other* than the reactive centres indicated by substitutions The principal reaction studied was catalytic hydrogenation which, as he pointed out bears some analogy to a biochemical transformation proceeding under the influence of an enzyme Fieser & Hershberg (1938) found that methylcholanthrene and 10-methyl-



1 2-benzanthracene tended to add hydrogen at positions (e.g. the 6 7 double bond of methylcholanthrene) other than the *meso* centres or other centres hindered by neighbouring rings or by the presence of substituents (IX X)

Boyland & Weigert (1947)² have already indicated how a carcinogenic hydrocarbon may first of all combine with an



enzyme or with other tissue-constituents such as ascorbic acid or purines through the positions of prime reactivity, and have shown the way in which a hydrocarbon can be altered in the body to give neutral water-soluble substances by addition of the elements of hydrogen peroxide at positions of only secondary reactivity From the data available on the fate of carcinogens *in vivo* it therefore appears that the metabolism-reactions involve attack at centres other than those specially liable to substitution, and Fieser regarded this situation as comprehensible on the hypothesis that the carcinogen is subject to two reactions proceeding by different mechanisms one responsible for the induction of malignant growth and the other leading to detoxification

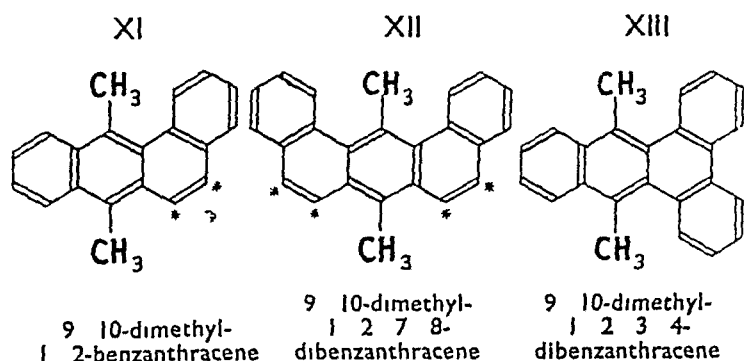
" the assumption that the metabolic change follows a fundamentally different reaction mechanism from the postulated substitution reaction of carcinogenesis seems necessary in order to account for the fact that the attack occurs at a part of the molecule different from that involved in substitutions

That it may in fact be possible to dissociate detoxication mechanisms from those which are specifically concerned in the process of carcinogenesis is supported in evidence of a different kind described by Crabtree (1947)³ Crabtree showed that the usual course of carcinogenesis might be impeded first by certain chlorine compounds which he

² [B.M.B. 968]
³ [B.M.B. 966]

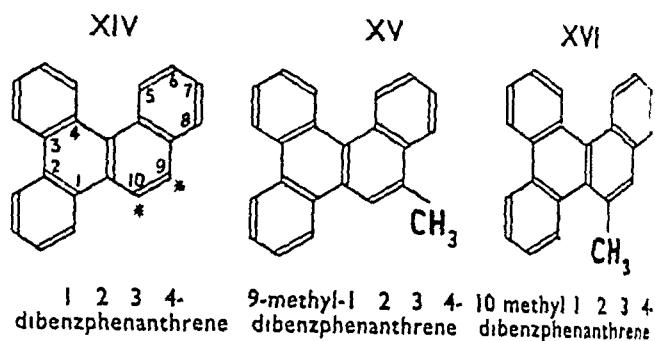
suggested could act through condensation with SH-containing components so as to impair enzyme systems dependent on intact SH groups, by bromobenzene, by another class typified by the unsaturated maleic and citraconic acids, which form addition products with SH-containing compounds and disturb the sulphur metabolism of mouse skin by fixation of glutathione, and by naphthalene, anthracene and phenanthrene, which are excreted as mercapturates. Since these four groups appear to possess only one common feature (their action upon sulphur metabolism), and since there is no evidence that sulphur is involved in the detoxication of carcinogens, Crabtree suggests that it may be some interference with sulphur metabolism, by preferential combination, which tends specifically to inhibit the mechanism of carcinogenesis.

In the attempt to define the essential structural requirements for carcinogenicity, Robinson (1946) has recently suggested that the weight of evidence indicates the possibility of reaction at an activated phenanthrene-type bridge in the great majority of cases. But again there are certain apparent exceptions, more than one mechanism may be involved and Robinson made clear his unwillingness to advance even a provisional hypothesis until more facts had been gathered. There are equally, however, several examples not merely consistent with such a view, but remarkably striking and suggestive in the relationships they show. The extreme carcinogenicity of 9, 10-dimethyl-1, 2-benzanthracene (XI) is a clear illustration that unsubstituted *meso* positions are not essential for activity, and it is of great interest in the present connexion that 9, 10-dimethyl-1, 2, 7, 8-dibenzanthracene (XII) has now been found by Berenblum (1946) to possess marked carcinogenicity, in contrast with 9, 10-dimethyl-1, 2, 3, 4-dibenzanthracene (XIII) which is completely devoid of such activity.

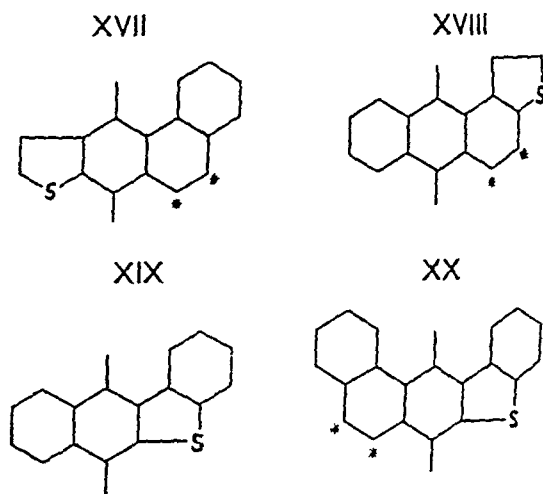


These examples are in keeping with the view that an essential requirement may be the phenanthrene double bond and that the 9- and 10-positions of phenanthrene (shown in XI and XII by *) must be unsubstituted, it also appears that the reactivity of these positions may be enhanced (or competitive reactivity reduced) by appropriate substitution elsewhere. Another critical case, also in agreement, has recently been described by Harris & Bradsher (1946) in an astonishing contrast between the high carcinogenic activity of 1, 2, 3, 4-dibenzphenanthrene (XIV) and the total absence of activity in either the 9-methyl (XV) or 10-methyl (XVI) derivatives.

One further method of attack, applied by Robinson, has been to test substances analogous with known carcinogens in that a benzene ring is replaced by the isosteric thiophene



nucleus. In 9, 10-dimethyl-1, 2-benzanthracene itself there are three benzene nuclei which might be replaced in this way, and in two of these cases (XVII, XVIII, Fieser, 1941) the products are already known to be carcinogenic. The third isomeride, which is of greater significance in that the phenanthrene bridge is here replaced by sulphur (XIX), has now been prepared by B. Tilak (1946), and it is certainly of interest not merely that this compound is non-carcinogenic by subcutaneous injection in mice, and seems to be only weakly active on painting, but that high potency again emerges in the benzo-derivative (XX), where the phenanthrene double bond is once again a feature.



The apparent importance of the phenanthrene double bond, even if it is not completely determining in its influence upon carcinogenic activity, finds a parallel in the ethylene bridge of the aminostilbenes (*infra*). Between these structures there is a high degree of similarity not merely on purely chemical grounds, but also in the way in which substitution, modification or total replacement leads to annulment of the biological activity of the molecule as a whole. So far as the growth-inhibitory effects of the aminostilbenes are concerned, such activity disappears when the ethylene bridge is extended to three or four carbon atoms when it is reduced, when either or both hydrogen atoms are substituted by an alkyl group, when either =CH-group is replaced by a nitrogen atom, or when the whole bridge is replaced by oxygen or sulphur.

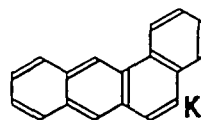
It is still too early to say whether the same strict rules govern the carcinogenicity of the aminostilbenes, even though

these were discovered as the direct outcome of a study of their inhibitory properties, to the extent however that is permitted by the results obtained so far, it can be said that the correspondence is complete. In the aminostilbenes it would seem to be a necessary condition although clearly not a sufficient one that the molecule should be capable of assuming a quinonoid disposition with an electron-donating group in one ring conferring a high degree of negative polarity in the other, and the outstanding feature being the necessity for unsubstituted hydrogen atoms in the ethylene bridge and at the *p'* position. Such a system would appear not merely to contain a structure in the ethylene bridge which is analogous with the phenanthrene double bond in the cyclic hydrocarbons but to possess electronic characters which are produced in condensed systems of benzene rings by rather different means. Further the amino-diarylethylenes present certain advantages in their comparative simplicity and in the relative ease with which one may hope to establish a connexion between constitution and activity. Finally the changes they are likely to undergo in the body—a few of which are indicated in XXI–XXIII for 4-dimethylamino-stilbene in comparison with known steps in the oxidation of *p*-aminophenol (XXIV–XXVII)—are again such as might be expected to interfere with the oxidative mechanisms of the cell.

4 Energy States in the Carcinogenic Molecule

The above relationships gain further interest from recent attempts to establish a connexion between electron distribution and chemical reactivity on the one side, and carcinogenicity on the other in the condensed unsaturated hydrocarbons. Otto Schmidt (1938, 1939a, 1939b, 1941) was the first to compare the electronic density of the *meso* regions of

XXVIII



certain carcinogenic substances with that in related non-carcinogens and on the basis of this comparison he postulated that it is a necessary condition of carcinogenic activity that the density of such regions should exceed $0.44e/\text{\AA}^2$, in particular he further suggested that the activity of a carcinogen is due to the electro affinity of its excited state facilitating a quantal change in neighbouring molecules. More recently A & B Pullman (A Pullman 1945, 1946a, 1946b, B Pullman 1946, A & B Pullman 1946) and Martin (1946) have obtained supporting evidence of this conception through a quantum mechanical treatment (with Daudel) which permits a calculation of the density of π -electrons for a given structure (in chrysenes, benzantracenes and benzacridines) by means of which it is claimed that a relation can be formulated between carcinogenicity and the electronic density of the region K (XXVIII) the density-threshold below which a substance ceases to be carcinogenic being $1.292e$.

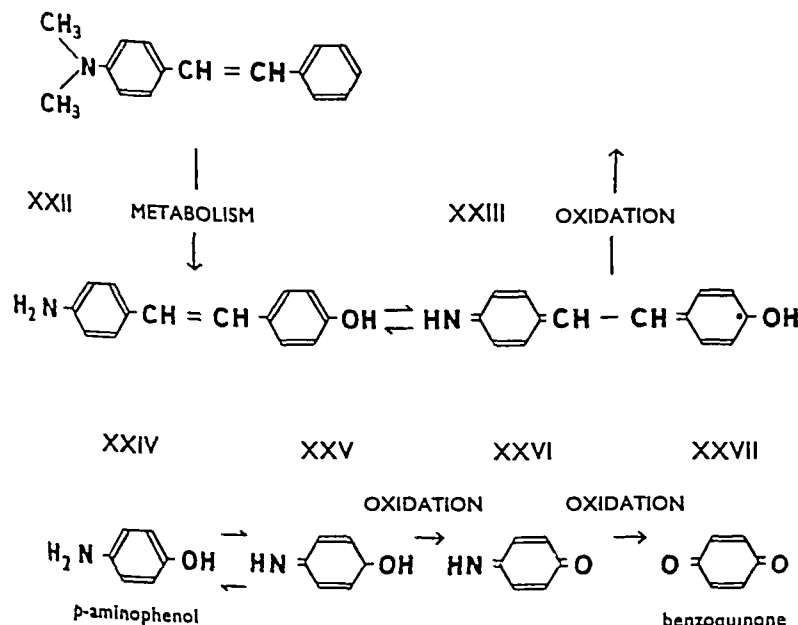
The Pullmans also state that it is not the position of the K region which is of first importance, but its specific character, and that it may appear at other points of the molecule and still possess the same function, hence, while their work would seem to confirm in the main, and on a quantitative basis, Schmidt's theory of the

relation between the carcinogenic power of a molecule and the existence within this molecule of a region rich in mobile electrons, it is less in agreement on points of detail such as the position of the active region, and the influence of substituents. Pacault (1946), by measurements of magnetic susceptibility, also indicates certain electromeric structures, the existence of which appears to be correlated with the particular biological property of carcinogenicity, and Daudel (1946a, 1946b), like Schmidt, has envisaged the molecular alterations which might proceed from the proximity of a region rich in π -electrons to certain regions of protein molecules. These views, that the concentration of π -electrons is the preponderant cause, if not the only one, of the carcinogenic property, may possibly represent an over-simplification, and are in any case subject to further scrutiny and test. But there is no doubt they are symptomatic of the need for a deeper understanding of the manner in which carcinogens operate, and that they would if confirmed, as Daudel says, effect a remarkable liaison between biological problems on the one hand and the most abstract regions of pure science on the other.

5 Biological Considerations

Turning next to the biological plane it may immediately be claimed that purely physiological methods have been surprisingly successful

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in the attempt to decipher the mechanisms of carcinogenesis, and have at the least made a full contribution. It is of course upon biological methods that we must depend for the primary data of carcinogenesis, and these may briefly be reviewed before proceeding. In the first place, we have no reason to doubt the view, and every reason to support it, that the process is one which is local in origin, and is due to direct action of the carcinogen or its products upon the affected cells. That chimney-sweep's cancer is due to local contamination of the skin with soot, and not to any "disease of the habit", was clearly recognized by Pott in 1775, although the local or constitutional origin of cancer in general continued to be debated a hundred years later, as at a famous meeting of the Pathological Society of London in 1874, when Sir James Paget was still interpreting cancer as a disorder of the blood, in opposition to Sir William Gull, Arnott, Hutchinson, Moxon and others who maintained its strictly local origin. We now know that, while constitutional and genetic factors can greatly influence susceptibility to cancer, and may even determine the site of its spontaneous occurrence, the disease is one of the individual cell as a separate organism and with no relation to the needs of the body as a whole. It is this which gives cancer its unique position in pathology, accounts for its intractable nature, and explains its growth, in Paget's words "irrespective of the maintenance of the rest of the body, discordant from its normal type, and with no seeming purpose" (Paget, 1853).

As to the nature of the transformation from the normal to the malignant cell, and the manner in which the carcinogens effect it, no interpretation can be sufficient which fails to take account of the great diversity of tumour-producing agents. Indeed, one of the most striking features of cancer is the multiplicity of its experimental causes, including not merely the variety of chemical compounds already considered, but physical agents such as ultra-violet rays, x rays, and the radiations emitted by radium and other radio-active elements. Such apparent lack of specificity may be merely superficial, and it has already been shown that many of the chemical carcinogens have more in common than appears. Further, since the pathological end-result in all cases is the same, it is probable that the cellular processes involved are not completely dissimilar and may in fact have an identical basis, the same general types of interference with function being induced by a wide range of causes. This view is supported by the fact that different carcinogenic influences may be interchanged (Berenblum, 1930) or summated (Hieger, 1936), during the period of tumour-induction, a result which is to be expected if cancer can result not only from a single chain of abnormal events but from several which lead by different routes to a final common path. Foulds (1945) has compared the seeming non-specificity of carcinogenic agents with the non-specificity of agents which lead to the liberation of the H substance and Sir Thomas Lewis's "triple response", and the writer (Haddow, 1938) also pointed out that the basis of non-specificity in cases of this kind is probably the extremely limited number of possible physiological responses. As regards division, for instance, a normal cell can react in only one of three ways: (a) by continuing growth at a temporarily increased or decreased rate, (b) by ceasing growth, or (c) by undergoing malignant change so as to divide at a permanently increased rate.

Although our central problem is the means by which so many carcinogens produce malignant transformation in

somatic cells, it is certain that this is only a special case of the origin of discontinuous cellular variation in general, e.g. in bacteria, protozoa, fungi and plants. It was therefore suggested by several workers (Lacassagne, 1936, Haddow, 1937)—and has been fully confirmed—that a study of the physiology of unicellular organisms, and particularly of bacteria, might be of unique value in deciphering the fundamental principles of such variation. As the result of experiments along these lines the writer (Haddow, 1937) concluded that the sources of discontinuous variation are mainly environmental in origin, and that its induction in a given character depends upon two main requirements: (i) a cell which is inherently capable of variation, (ii) a source of environmental interference with the character in question. Special attention was given to the environmental conditions governing the origin of variants with a permanently increased growth-rate, when it was found that such variants are produced not by any process of direct growth-stimulation, as might be expected, but appear as a sequel to a long continued period of growth-repression.

It therefore seems that when the growth of a potentially variable organism is continuously inhibited by a process which allows a sufficient proportion of the affected cells to survive, a relatively small number may undergo an irreversible change in their metabolic properties in virtue of which they are then able to achieve active multiplication in an environment which makes this difficult, or even impossible, for their parent cell.

That a general principle of this kind might well apply to the induction of tumours was supported by the finding that the great majority of a long series of chemical carcinogens produced a rather characteristic inhibition of body-growth in the rat, and that such activity was mostly absent in a similar series of related non-carcinogenic compounds (Haddow, Scott & Scott, 1937, Haddow & Robinson, 1937, 1939, Badger, Elson, Haddow, Hewett & Robinson, 1942). The main feature of the inhibition brought about by the carcinogenic hydrocarbons is its relative prolongation, and it is almost certainly significant that x rays and radium, which are also carcinogenic in certain circumstances, are equally capable of producing a similar inhibition under the same circumstances, the most suitable conditions being (a) continuous exposure to a weak source of radiation (Ross, 1936), or (b) prolonged or repeated exposures. From the writer's results there seems little doubt of a substantial correlation between carcinogenicity and growth inhibitory power, and it therefore seemed a real possibility, as in the case of x rays and radium, that the mode of action of chemical carcinogens might well be indirect, and that they could operate by retardation of the growth of normal cells, the latter eventually reacting to give a new race of cells with an increased rate of fission. While the correlation on which this view is based seems sufficiently strong to justify it, undoubted exceptions occur which, if they are not enough to invalidate the hypothesis as a whole, indicate that we should regard it as a general approximation. Additional confidence in this view was, however, given by the discovery first of all that various derivatives of 4-aminostilbene possess such inhibitory properties *par excellence*, and only later that these compounds are, in fact, endowed with carcinogenic properties of an exceptionally interesting kind—an association which would seem to be more than one of chance alone.

Many other workers from time to time have also regarded the malignant cell as representing a new race or strain, and as a discontinuous and irreversible somatic variant (Hauser, 1903, Menetrier, 1926).

The main interest of the present argument is the hint it gives of the *origin* of such variants—that cancer cells arise and commence their career of proliferation as an adaptation to conditions which impair the growth of normal cells. Here again the conception is by no means new, and it is remarkable how one or other expression of it recurs again and again throughout the whole literature. Thus Minot (1889), who was among the first to study the progressive decline in the rate and power of growth from the beginning to the end of life, maintained that the retardation of growth accompanying senescence is the stimulus which inaugurates discontinuous growth or proliferation. If interference with growth is an essential prelude to tumour-formation, it is not surprising that tumours arise in growing tissues essentially, and only comparatively rarely from obsolete or obsolescent structures or from highly specialized organs such as the heart and large vessels, voluntary muscles and nerves. This too has been long recognized, for example, by Roger Williams (1908)

‘in all such instances proliferous cells are scanty or absent, and it is to this peculiarity that their comparative immunity from tumour growth may be ascribed. The growth of cancers, like discontinuous growth in general, of which it is but a particular case, is distinctly related to the decline of growth of the body in general, and especially of the particular local tissues. Hence, while the forces of growth, development and reproduction are in greatest activity—during the period of pre-natal life, infancy, childhood, adolescence and even adult age—the tendency to this disease is comparatively small. In both sexes, it begins to be of great frequency in the post-meridian period. Thus the tendency waxes, as the developmental and reproductive activities wane, when growth declines, new centres of development are apt to arise, and growth tends to become discontinuous’

Adaptive variation in relation to the origin of tumours has also been described by many other authors (e.g. White, 1913), and Bang (1928) was among the first to recognize that since the cancer cell arises from the normal cell, its behaviour must be considered in relation to its environment, pointing out that most carcinogenic agents probably act by injury. Lewis (1935) also suggested that malignant cells are new cellular types or species derived from normal cells which have been altered by environmental influences or agents of one sort or another, and Beclere (1934, 1936), discussing the role of γ radiation in carcinogenesis, opined that it is a slow destruction of the activities of the cell, rather than direct excitation of its growth-capacity that terminates in malignancy. Wolbach (1936, 1937), attempting to ascertain what processes are initiated by carcinogenic hydrocarbons prior to the development of tumours, apparently regarded the primary action as destructive.

‘no evidence was found to support a theory that any one of the chemicals employed owes its carcinogenic property to direct stimulation of cell growth’

Similarly Witts (1936) in a discussion of neoplasia of the blood-forming organs in relation to toxic agents such as benzene, x rays and radium referred to the question “whether arrest of the normal development of the cells does not sometimes lead to the uncontrolled proliferation of leukaemia”

6 Carcinogenesis and Cellular Nutrition

Still deeper insight into the mechanism of carcinogenesis has been gained by the application of biochemical in contrast to purely physiological methods. Boyland (1932) was among the first to study the action of the carcinogenic hydrocarbons

and their oxidation products upon enzyme systems *in vitro*, and there is now a vast literature which in many ways suggests that the damage produced by the carcinogen in the normal cell may be correlated with enzyme poisoning, and that the resulting cell adaptation, which we call malignant change may be reflected in the appearance of newly developed “rogue” enzymes upon which the newly acquired growth-properties may possibly depend.

One of the most remarkable developments in cancer research in the past few years has been the recognition that the carcinogenic action of azo compounds, and particularly of dimethylaminoazobenzene, is greatly influenced by the diet (Mori & Nakahara, 1940, Mori, 1941, Sugiura, 1944) and especially dependent upon its content of protein, and the great bulk of such enzyme studies has been carried out with this exceptionally favourable material Rhoads (1940, 1942a, 1942b) and Rhoads & Kensler (1941), in a study of the induction of hepatic cancer by administration of dimethylaminoazobenzene to rats taking a diet of brown rice and carrots, found that supplementing this diet with yeast- or liver-extract in adequate amounts completely prevented the development of tumours, the protective factor being none of the constituents of the vitamin-B complex then described. The effect of feeding the carcinogen to animals taking the unsupplemented diet was an inhibition of the activity of at least two enzyme systems, cocarboxylase and cozymase, thus producing what these authors considered a conditioned or secondary deficiency disease. On the other hand, the development of the mutation which characterizes the malignant cell was accompanied by the appearance of an oxidizing system insusceptible to the inhibitory effect of the toxic metabolic products of the carcinogen, and Rhoads and Kensler looked on their results as the first demonstration that cancer tissue evoked by a chemical carcinogen possesses an oxidative system immune to the inhibitory action of that carcinogen or of its metabolic products.

We have already seen that the emergence of a malignant tumour has many analogies with discontinuous variation in bacteria, and there is little doubt that the phenomenon—probably on account of its fundamental and general nature—has features in common with such processes as *smooth*→*rough* variation in bacteria, and with acquired drug-fastness in bacteria and protozoa. A similar conception has lately been formulated by Lederberg (1946), on the basis of the studies by Beadle, Tatum and others of the genetic control of biosynthetic reactions in the fungus *Neurospora*. Since field strains of *Neurospora* will grow on media containing only sugar, salts and biotin, it is concluded that the fungus is capable of synthesizing all other essential metabolites. As the result of mutation of single genes, the capacity for synthesis of different compounds (e.g. leucine) may however be lost—a process which possibly accounts for the differentiation and nutritional requirements of higher forms. It is obvious that the growth of the “*leucineless*” modification of *Neurospora* would necessarily be regulated by the concentration of leucine available to it externally. Exceptionally however, a gene-mutation may once again lead to the capacity to synthesize such a metabolite and Lederberg therefore correlates normal tissue cells with a culture of “*leucineless*” *Neurospora*, and the malignant cell with a variant having a newly acquired or re-acquired capacity to synthesize an essential metabolite otherwise only available in regulatory amounts.

The present writer has very recently encountered a remark-

able effect of the naturally-occurring pigment xanthopterin (*syn* uropterin) upon the kidney of the rat, which is extremely reminiscent of a similar mechanism. Administration of this compound induces an increase in kidney-size due very largely, if not entirely, to a direct stimulation of mitotic activity and cell-division in the tubule epithelium. The effect appears highly specific and is automatically reversible—almost certainly when the administered xanthopterin has been excreted. Although a great deal of necessary investigation has still to be completed, this situation is highly suggestive of a device by which the normal growth and occasional hypertrophy of the kidney may be completely regulated and controlled, by its dependence upon an essential factor which the organ is unable to synthesize and which must be supplied from elsewhere. If this mechanism should be fully substantiated, it is clear that two further questions will arise, one affecting its general validity, and the second concerning its implications for the origin of tumours.

Is it possible that the co-ordinated growth of all the normal tissues similarly depends upon the supply of essential and specific growth-factors, the chemical variety of which may reflect the chemical basis of cellular differentiation? If so, may the chemical carcinogens first of all impede the growth and protein synthesis of normal cells by restricting the utilization or access of such essential metabolites? In such a case, we may yet be able to correlate the new and adaptive growth-properties of the cancer cell, and especially its power of *continued* and unregulated growth, with the acquisition of a genetic property to synthesize an essential growth-factor, or factors, previously supplied from an external source. On this view, the transformation from normal to malignant would represent a change from a fastidious or comparatively-exacting cell to a variant which is unexacting and self-sufficient, and the autonomy of the cancer cell, which has long been known as its chief attribute on purely biological grounds, would receive its explanation in terms of cellular nutrition.

The past fifteen years have seen enormous advances in our understanding of the specific nutritional requirements of bacteria, protozoa and fungi, of the extent to which they are dependent upon inherent synthetic capacities on the one hand, and the supply of preformed metabolites on the other, and of the ways in which these properties may be altered by environmental changes and induced mutation. An indication has already been given that these principles have a relevance for biology far transcending their application to unicellular and freelifing organisms alone, and we have seen how they are not merely suggestive but of practical value in increasing our comprehension of the analogous situation in the origin of cancer. They also point the way to the next stage, namely, systematic investigation of the specific growth-requirements of malignant cells, in comparison with those of their normal prototypes, *in vitro*. If such an investigation is bound to be more arduous on technical grounds, it is certain to gain immeasurably from the experience already accumulated from nutritional studies in protists and fungi.

7 Energetics of the Malignant Transformation

Possibly the most striking single feature of the cancer cell is its high stability, as shown by the manner in which its newly-acquired properties are transmitted and maintained, quite indefinitely and with no sign of reversion, in the course of serial transplantation. From this it is clear that, once a

given carcinogen has effected the malignant transformation, its continued presence is no longer necessary for the subsequent autonomous growth of the tumour. In many ways the processes of cell division are reminiscent of a chain reaction or self-propagating mechanism which varies in the degree of control to which it is subject, and it may be that the new configuration of properties which distinguishes the malignant cell from its normal precursor can be expressed in terms of a different energy-level. Highly suggestive of such a relation is the ease with which the normal cell may be converted into a malignant form, in contrast with the impossibility (thus far) of effecting a change in the reverse direction. It is also of the greatest significance that, while the normal and malignant cell-types have their own levels of stability, and are therefore discontinuous in their properties, transition from the former to the latter is by way of intermediate forms of high instability. Berenblum (1947)¹ and others have shown how carcinogenesis in the skin proceeds from the normal epithelium first to an early non-specific hyperplasia, secondly to a specific pre-neoplastic hyperplasia, and then to the emergence of papillomata, and how later stages can be recognized in the progressive growth of such papillomata, their conversion into carcinoma, and the uncontrolled growth of the latter. While the earlier stages in this sequence may be reversible (even in some cases to the extent of regression and disappearance of warts when the carcinogen is withdrawn), the later steps are quite irreversible and take place equally well whether exposure to the carcinogen is continued or not.

Considerable interest in the energy relations underlying such changes has been evoked by Schrodinger's recent account (1944) of quantum theory in relation to biology and genetics. Schrodinger was led, from a study of the high degree of permanence and durability of the gene material on one hand and its discontinuous mutation on the other, to suggest that such phenomena may be explained in terms of quantum theory, and that mutations may in fact be due to quantum jumps in the gene molecule. The high degree of permanence of the gene material has a corollary in the comparative rarity of mutation, but the so-called natural rate can be increased to a high multiple by irradiation with x rays or gamma rays, the mutations produced differing in no way, save their number, from those that occur spontaneously. And there is an energy relation

"the experiments on X-ray-produced mutations give the impression that every particular 'transition', say from the normal individual to a particular mutant, or conversely, has its individual 'X-ray coefficient', indicating the percentage of the offspring which turns out to have mutated in that particular way, when a unit dosage of X-ray has been applied

Schrodinger then recapitulated the laws governing the induced mutation rate—that the increase is exactly proportional to the dosage of radiation, and that the coefficient of increase remains unaffected by wavelength provided that the same dosage, in *r* units, is applied. Mutation appears to be due to a single event, represented by an ionization or similar process, occurring within some critical volume of the cell. For the size of this critical volume Schrodinger followed Delbruck (Delbruck, Timofeeff & Zimmer, 1935), who arrived at an approximate size of only ten average atomic distances cubed comprising therefore 1,000 atoms. That such a group of atoms is much too small to display exact statistical laws, and so conform to statistical and

¹ [BMB 965]

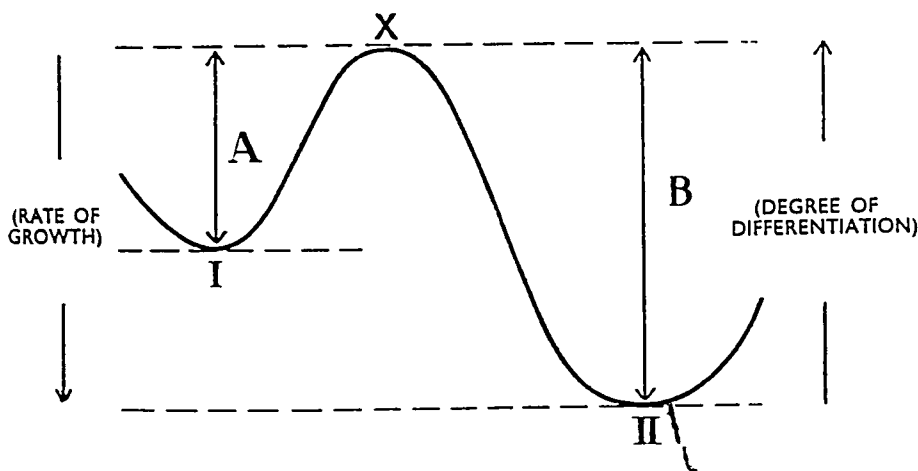


FIG 1

Probable energy barrier (X) in the transition from the normal to the malignant state (see text and Schrodinger p 55) A=Minimum energy required to effect the change I (normal) \rightarrow II (malignant)

classical physics is in contrast with the known permanence and stability of the gene material but in Schrodinger's view the explanation is wholly supplied by quantum theory. While a body on the large scale changes its energy continuously, a sufficiently small system is bound by its very nature to possess only certain discrete amounts of energy (its peculiar energy-levels) and the event of transition from one state to another is the quantum jump. If the second state or configuration has the greater energy (i.e. is a higher level) the system must be supplied from outside with at least the difference of the two energies to make the transition possible. To a lower level it may change spontaneously emitting the surplus of energy in radiation.

This conception requires to be amended for those cases in which free passage between two levels may be obstructed even from a higher to a lower level. There are no spontaneous transitions from one state towards another, when the two configurations are not neighbouring and transition can take place only over intervening configurations that have a greater energy than either of them. Most significant such "isomeric" transitions are those of the greatest importance for biology.

Transitions with no threshold interposed between the initial and the final state are entirely uninteresting, and that not only in our biological application. They have actually nothing to contribute to the chemical stability of the molecule. They have no lasting effect; they remain unnoticed. For, when they occur, they are almost immediately followed by a relapse into the initial state, since nothing prevents their return.

These relations at once recall the familiar and similar distinctions between fluctuating and permanent biological modifications, between variants that are irreversible and those that return to the parent form with greater or lesser ease. For all practical purposes the origin of cancer is the outstanding example of an irreversible cell variation. It does not however follow that this is necessarily so in an absolute sense and Fig 1 shows in schematic fashion after Schrodinger the energy-barrier (X) interposed between the stable states I (normal) and II (malignant) with the minimum energy (A) required to effect the change from energy-level I to level II, it is obvious that amounts of energy less than this minimum will suffice only to produce impermanent changes which revert to the normal. It would also appear,

theoretically at any rate that reverse transition from malignant to normal may be achieved by the application of a minimum amount of energy greater than that required to change from the higher to the lower level, as to how much greater nothing is known. In addition the transition from normal to malignant is frequently marked not only by an increased growth-rate but also by loss of cellular differentiation. This inverse relation is also indicated in the figure although it is far from being either simple or invariable.

An interpretation along these lines has almost certainly a close connexion with other features in the mode of action of carcinogens. For instance recent work on the metabolism of 3,4-benzpyrene (Boyland & Weigert 1947)⁵ hints that it is not the hydrocarbon itself or even one of its metabolites, which is the proximate carcinogenic agent, but rather the energy released during the transformation from one metabolite to another. Here too may possibly lie the true significance of the allegedly characteristic electronic properties of the carcinogenic molecule. Finally it may provide a link between the carcinogenic action of x rays, gamma rays, ultra-violet radiation and chemical compounds in that all these agents may be, as Daudel has suggested (1946b) sources or carriers of energy in such a form as can readily interfere with the normal growth of the cell. A similar argument has recently been used by Latarjet (1946) from a comparison between ionization and molecular activation in the primary action of radiations on micro-organisms. Highly ionizing radiations on the one hand and ultra-violet radiation on the other, are found to produce lesions so similar that it is impossible to decide from mere inspection the nature of the stimulus which provoked them and it is suggested that what they perform in common is to deliver to the appropriate location in the cell an amount of energy sufficient to produce an identical primary effect.

les processus de liberation de cette energie seraient differents, mais l'effet primaire serait le meme. En d'autres termes l'ionisation et l'activation moleculaire induisent la même modification chimique initiale.

From all these varied developments it would appear we are gradually approaching an understanding of cell variation in terms of the energies involved. Although an immense

amount remains to be done, there can be no doubt of the profound significance of any such achievement, not only for the cancer problem but for biology as a whole

8 Relation to the Viruses of Chicken-sarcoma

Any complete solution of the mode of action, such as we hope to achieve in the future, must make clear the relation between chemical carcinogens and the tumour-producing viruses. The beginning of modern experimental research in cancer, in the latter part of the nineteenth century, coincided with the rise of bacteriology. From that day until this, and very largely for that reason, there has always existed a school of thought which seeks to interpret the origin of cancer as due to a process of specific infection. In its first phase, this belief was based not on evidence but on intuition, and was only later followed by deliberate attempts to isolate and identify the causal agent which it was felt—and which in many quarters it is still felt—must be present. Between forty and sixty years ago, this work merely resulted in a depressing catalogue of allegedly specific pathogens—bacteria, protozoa, yeasts and fungi—and Schaudinn stigmatized this period as the most melancholy chapter in the whole history of the subject. Nevertheless, the logical possibility still remains, and must therefore very willingly be admitted, that the etiology of cancer may in some way be bound up with processes of infection, and particularly with virus infection.

Nowadays, however, the general thesis rests on evidence of a very different kind, dealing particularly with the filterable agent of sarcomata in fowls, of which the virus of the Rous chicken-sarcoma is the best known example, with the milk factor involved in the causation of breast cancer in mice, and with Shope's papilloma virus in the rabbit.

On the other hand, and opposed to any general infective theory of causation, is the school which senses that the neoplastic change has in its very nature something fundamental in biology, that it is a kind of change to which almost every type of cell in nature is liable in appropriate circumstances, and that it is far more profound than could depend upon infection in the bacteriological meaning, by independent and specific parasitic micro-organisms. Thus, the great mass of fact shows that processes of infection in the natural history of cancer are exceptional (that is, so far as we know), and not likely to be an indispensable feature of the induction of tumours. Contrariwise, we already have the certain means of producing a great variety of experimental tumours at will, by the chemical carcinogens, in circumstances which assuredly do not require us to introduce the conception of a ubiquitous virus.

The fascination of the present situation is that there is no difference of opinion on the facts themselves. There is no debate concerning the remarkable properties of the chemical carcinogens, there is no question that an agent is transmitted in the milk, in mice of high liability to mammary cancer, which largely determines the incidence of the disease in subsequent generations, there is no denying the causation of the Rous tumour by a virus-like agent. Differences arise only over the interpretation of these phenomena, which to some seem mutually incomprehensible, and to others even irreconcilable. But no one of these facts can invalidate any other, and it must therefore be our purpose not to foster an antithesis between one school and another, but to seek a synthesis.

The filterable agents of the avian sarcomata are submicroscopic particles extractable from the cells of such tumours, the Rous agent being the most familiar example. Tumours arising after inoculation of this and similar agents are derived from infection of the corresponding normal cells of the recipient host, and the salient features of this action are, first, that conversion of the normal cell to the malignant form may take place at once (in contrast to the action of the chemical carcinogens), and, secondly, that the new tumours so induced usually conform in the minutest detail with the growth from which the agent was obtained, and usually continue in their turn to produce further large amounts of the specific virus. From immunological experiments (Amies, Carr & Ledingham, 1940) the Rous agent appears to contain (in addition to a specific antigen) a second antigen which is also present in normal fowl-tissue. This remarkable serological property, coupled with intense specificity, and the apparent absence of any epidemiology whatever, have always supported the conclusion that the Rous and allied agents arise intrinsically.

In approaching this matter, it seems that there is no likelihood whatever of success if we restrict ourselves to the traditional methods of bacteriology or of cancer research alone. The net must be cast much wider, and advances are in fact already being made in general cell-physiology, usually without any direct reference to cancer or viruses, to which we must pay great attention and which offer the prospect of elucidating some at least of these problems. These advances now constitute nothing short of a revolutionary view of the importance of the cytoplasm, as distinct from the nucleus, in cellular growth and heredity, pointing directly to a conception of genetic determinants located in the cytoplasm, they are of the greatest interest to students of cancer who had been independently considering the possibility, for other reasons, that malignancy is due to an alteration not necessarily restricted to the nucleus, but affecting the cytoplasm as well (Haddow, 1944).

Perhaps the most apposite case is that described by Sonneborn (1943), in what must be regarded as one of the most significant biological papers of the past ten years. Sonneborn studied two heritable characters known as "killer" and "sensitive" in different races of *Paramecium aurelia*. The physiological situation is that fluid in which the killer race has lived kills individuals of the sensitive races, and that when pure races of the two types are crossed, the killer clones are found to derive their cytoplasm from the killer parent, and the sensitive clones are those with cytoplasm derived from the sensitive parent. This phenomenon was next shown by Sonneborn to be not merely a case of cytoplasmic inheritance, but due to the continued production of a cytoplasmic substance under the influence of a single gene known as K. The law governing this relationship was defined as follows:

"Addition of the cytoplasmic determinant to an organism lacking the character dependent on it, but containing the required gene, results in the continued production of the cytoplasmic substance, in the development of the character determined by the combined presence of gene and cytoplasmic substance, and in the hereditary maintenance of the character in successive generations."

The parallel between this relationship on the one hand, and the propagation of the Rous sarcoma by virus on the other, is certainly remarkable, on the assumption that the Rous agent may indeed be a particle derived from or located in the cytoplasm—in other words, that it is a plasmagene. For

this view there is in point of fact a good deal of support from the physical and chemical resemblances between the Rous agent and the sub-microscopic microsomes of Claude (1938a, 1938b, 1939, 1943a, 1943b), which are normally found in the cytoplasm.

If then we admit that this may be a reasonable and suggestive hypothesis, Sonneborn's law may be paraphrased for the special case of the Rous virus somewhat as follows "Penetration of the mutant plasmagene into the cytoplasm of a susceptible normal cell—that is, a cell which lacks the character of malignancy which is partly dependent on it, but which contains the required gene—results in the continued production of the cytoplasmic substance, that is the virus in the development of the character of malignancy determined by the combined presence of gene and virus, and in the hereditary maintenance of malignancy in successive cell generations "

In other words, there seem to be no differences of fundamental principle, between the activity of the Rous agent and the behaviour of a mutant plasmagene, and this suggestion if correct, would account for the individual specificity of the fowl sarcoma agents by which each transmits to the new host the characters of that particular tumour alone from which it was obtained

Although our eventual aim must be a correlation, as complete as possible, between all the available facts, it is only within the past year or two that we have had any inkling of the way in which this might be achieved. We have already considered firstly the association between the property of carcinogenicity and the capacity of chemical carcinogens to produce a rather characteristic type of interference with normal growth, and secondly, the working hypothesis which then emerged, that the chemical carcinogens might operate by producing an interference with growth, of a kind to which the cells could adapt themselves only by an irreversible differentiation, which would automatically confer upon the new cell strain (that is, the induced tumour) a permanently-increased rate of division

Quite recently, Elson (Elson & Warren, in press) has found that this initial inhibitory action of the chemical carcinogens can be greatly reduced, or even prevented, by a diet sufficiently rich in protein. Particularly since it was already known that the experimental production of cancer of the liver by various azo compounds could be similarly delayed or again even prevented by administration of a high proportion of protein in the diet (*v supra*) we are beginning to consider whether the initial action of the carcinogenic hydrocarbons and other chemical carcinogens may not be to inhibit growth by depleting the cellular protein, by rendering it unavailable, or possibly by interfering with its normal synthesis, that the eventual emergence of the malignant cell may be achieved through an irreversible modification of protein synthesis and that it is this re-orientation which underlies the unregulated and permanently-enhanced capacity for growth

Starting from an entirely different approach, Crabtree (1947)⁶ has also found it tempting to speculate that a disturbance of enzyme function could lead, through the formation of a carcinogen-enzyme complex and by cellular adaptation to the emergence of a new type of protein with auto-synthetic properties. Bearing in mind the physical and chemical similarities between the Rous agent and the non-infective particles, may it be that the filterable agent is a chemical variant of a normally occurring particle, produced

through the action of a chemical carcinogen? Certainly this view can provide no explanation of the comparative rarity of cell-free transmission of tumours generally, but there is, on the other hand, a reasonable probability that elucidation of the nature of the Rous virus would furnish important principles applicable to cancer as a whole. This would certainly seem to be the opinion of Potter (1945), who from purely biochemical evidence has suggested that the uncontrolled growth of cancer may be the result of competitive interference between two autosynthetic proteins—one a normal enzyme protein and the other a modified form which could arise spontaneously from mutation, be produced by the action of carcinogenic chemicals, or be introduced preformed as a virus

In all these varied possibilities, we are constantly reminded of the point to which Stanley (1939) originally drew attention in the case of the plant viruses that the influence of such viruses can be likened to that of normal agents already present. In other words, the notion that the avian-tumour viruses are of intrinsic origin may be related with the view that many of the plant viruses are autocatalytic proteins of ultimate host-cell origin. There is a further aspect of the general problem which may prove of wider significance than any so far mentioned namely, the relation between plasmagenes and cellular differentiation (Rhoades, 1943). It has long been one of the puzzles of biology that, while all the cells of an organism presumably have the same genetic constitution in their nuclei, they nevertheless show wide morphological and physiological differences. These differences might be due to variations in tissue environment, but this is not the whole explanation, since many cells retain their main characteristics, at any rate in part, when they are transported or transplanted to another part of the organism. It is now possible to suggest that cellular differentiation of this kind may be determined by genetical particles in the cytoplasm. The production of different characters in cells with the same nuclear genes would thus be brought about by differential segregation of those cytoplasmic determiners at cell division. If the differentiation and rate of growth of both normal and malignant cells are controlled by particulate determinants in the cytoplasm may it be that the Rous agent functions by imposing a decreased level of differentiation, and hence an increased rate of growth upon the normal cell which it attacks?

* * * * *

Nothing can be more remarkable than the way in which these different trends and developments, some arising from cancer research itself and others from advances in biology generally, are gradually producing a unified picture in place of the two contrasting interpretations of the genesis of cancer. The ultimate solution of the origin of tumour viruses will no doubt be expressed in terms of enzyme and protein chemistry in a new sort of taxonomy which will doubtless require the powers of a chemical Linnaeus and a modern Darwin combined. But it already appears that all these varied findings are irreconcilable only on the narrow view and that there is a real prospect of deeper understanding if we change our viewpoint, and especially if we broaden it. Only in this way can we hope to follow the sequence as a whole, and to piece together all our facts, from wherever they come.

⁶ [BVB 966]

MODE OF ACTION OF CARCINOGENS *A Haddow*

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COCARCINOGENESIS

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In experimental studies on tumour production important information is sometimes obtained by testing the action of a carcinogen in combination with some other (physical or chemical) external agency. When the added treatment causes augmentation of tumour production (i.e. a higher yield of tumours or a shortening in the latent period) it is called *cocarcinogenic action*, when the result is an inhibition of tumour production it is called *anticarcinogenic action*. Though the term 'cocarcinogenic' seems at first sight unambiguous the need for careful definition becomes apparent when the subject is examined more closely.

For instance liver-tumour production in rats resulting from prolonged administration of *p*-dimethylaminoazobenzene occurs more readily when the diet is supplemented with biotin or fat and less readily when supplemented with riboflavin and casein¹. It is debatable whether one should regard the biotin and fat as cocarcinogenic and the riboflavin and casein as anticarcinogenic or whether it would not be more logical to regard deprivation of biotin and fat as *anticarcinogenic* and deprivation of riboflavin and casein as *cocarcinogenic*. In any event the conditions operating with remote influences (i.e. via the diet) may be different from the local application of a cocarcinogen at the site of tumour production. Hence the avoidance of the term 'cocarcinogen' for dietetic influences and the substituted use of such a term as 'procarcinogenic' (Du Vigneaud, Spangler, Burk, Kensler, Sugiura & Rhoads, 1942) seems fully justified².

A similar difficulty arises in connexion with the effects of solvents on carcinogenic action. It has been shown for instance that sarcoma production in mice occurs more readily with benzpyrene dissolved in olive oil than when mouse-fat is the solvent (Peacock & Beck 1938). Here again, the mouse fat might be regarded as anticarcinogenic (if the olive oil series is considered as the control) or alternatively the olive oil might be regarded as cocarcinogenic (if the mouse-fat series is considered as the control). In fact probably neither term is justified since the influence of the solvent on carcinogenesis may be due to modifications in the rate of absorption and elimination of the carcinogen, rather than to a direct effect on the tissues. A solvent may nevertheless prove to be a true cocarcinogen if augmentation of tumour production can be demonstrated by administering the solvent and the carcinogen separately over a different period of time³.

For the purpose of the present review cocarcinogenic action may be defined as an augmentation of tumour production resulting from a direct local effect on a tissue.

Cocarcinogenic Agents

The earliest demonstration of cocarcinogenic action was concerned with scarification of the skin. Deelman (1923) claiming that such treatment facilitated tar carcinogenesis. What is more generally described as 'the Deelman effect' arose under conditions of more severe scarification (or with actual incisions in the tarred skin) the subsequent tumours showing a tendency to become localized close to the healing or healed wound (Deelman, 1924, Deelman & van Erp, 1926). Though several subsequent investigators failed to confirm these results more recent work provides adequate confirmation (especially of the localization-effect) both in mice (Pullinger 1943, 1945a, b) and in rabbits (Rous & Kidd 1941, Mackenzie & Rous 1941, von Meyenburg & Fritzsche, 1943, Friedewald & Rous, 1944a, b). A similar localization-effect was observed at the margins of areas of freezing in tarred skin of mice (Berenblum 1929). Using a continuous form of mechanical irritation (sandpapering) subsequent to a period of tarring Ludford (1929) failed to observe augmentation of carcinogenesis in mice but more recently with dibenzanthracene as carcinogen and a stiff brush as a means of irritation Riley & Pettigrew (1945) obtained convincing evidence of augmentation. Subcutaneous fibrosis by threads placed under the treated skin also hastened skin carcinogenesis in mice (Orr 1934, 1935).

Many other factors have been tested from time to time, for cocarcinogenic action, including the effects of heat, ultra-violet rays, x rays, beta and gamma rays of radium and a host of chemical substances. Early examples of chemical cocarcinogens include (a) a basic fraction of creosote oil (Shear, 1938, Cabot, Shear & Shear 1940, Sall & Shear 1940 who introduced the term 'cocarcinogen'), and (b) croton oil and its active component croton resin (Berenblum, 1941a, b) perhaps the most potent cocarcinogen known for the mouse's skin though apparently without effect on the rabbit's skin (unpublished observation). Yet, in general the rabbit seems more responsive to cocarcinogenic action than the mouse as shown by the investigations of Rous and his collaborators (*loc cit*) in connexion with wound healing etc.

Analysis of Cocarcinogenesis

By no means all irritants elicit a cocarcinogenic effect. Indeed, some have pronounced anticarcinogenic effects⁴ while many fail to modify the carcinogenic response either way⁵. The accumulating data in the literature seemed at first full of inconsistencies and contradictions. Some of these contradictions could be attributed to different dosages used by different authors (Compare for instance the inhibitory effects of large doses of radiation (Cramer 1932) with the augmenting effects with small doses (Mottram 1937), and note how the anticarcinogenic chloro-compounds studied by Crabtree (1941) sometimes produced slight cocarcinogenic effects when tested with different concentrations of carcinogens).

⁴ [See article by H. G. Crabtree (*BMB* 966) —Ed.]

⁵ For detailed reviews on factors modifying carcinogenesis, see Rush 1944 and Berenblum 1944.

[See article in this number by J. W. Orr (*BMB* 975) —Ed.]
¹ Note: The term 'procarcinogenic' as applied to dietetic factors, must not be confused with 'procarcinogenic' — a stage in the process of carcinogenesis, as described below.

² [A more detailed consideration of anticarcinogenic action and of solvent effects on carcinogenesis will be found in the reviews by Crabtree & Dickens, respectively in this number (*BMB* 966 & 967) —Ed.]

The main source of discrepancies arose, however, from the complex nature of the mechanism of cocarcinogenic action. This became abundantly clear after segregating the conflicting experimental results according to whether (i) the irritant and the carcinogen were applied concurrently (i.e. the true *cocarcinogenic action*), (ii) the irritant was applied before the commencement of application of the carcinogen (*precarcinogenic action*), (iii) the irritant was applied after cessation of application of the carcinogen (*epicarcinogenic action*), or (iv) the irritant was applied to warts already established in an attempt to convert these into malignant tumours (*metacarcinogenic action*).

From such analysis (Berenblum, 1944), it transpired that while none of the non-carcinogenic irritants influences carcinogenic response when applied beforehand (i.e. when tested for precarcinogenic action), many of them did augment carcinogenesis when applied after cessation of carcinogenic action (i.e. manifested epicarcinogenic action), while a few also hastened conversion to malignancy (i.e. had metacarcinogenic effects). Croton oil, which is itself not carcinogenic, elicited these effects most strikingly (Berenblum, 1941a, b), though similar results were also obtained with mild freezing (Berenblum, 1930), scalding (Des Ligneris, 1940), radiation (Mottram, 1937), as well as wound healing (Deelman, Pullinger, and others, *loc. cit.*). All this evidence pointed to the conclusion that carcinogenesis in mouse-skin was a sequence of separate and independent processes, of which one—the preneoplastic stage of hyperplasia—was a specific response, distinct from ordinary reparative hyperplasia (Berenblum, 1941b, 1944).

Somewhat analogous conclusions were drawn by Rous and his associates, working on the effects of wound healing, and other forms of irritation, on rabbit skin, using tar (Rous & Kidd, 1941, Mackenzie & Rous, 1941), and later, methylcholanthrene or benzo(a)pyrene (Friedewald & Rous, 1944a, b) as carcinogenic agents. They drew attention to the marked tendency for induced warts in rabbits to regress, and for the same warts to reappear on subsequent stimulation (e.g. by further tarring, wound healing, application of turpentine, chloroform, etc.). Thus, despite the tendency for regression, the cells of the induced warts were irreversibly different from normal cells. This conception of a tumour existing in a sub-threshold state, requiring additional aid for progressive neoplasia (Rous & Kidd, 1941) was, in a later publication (Friedewald & Rous, 1944a), formulated in a more positive manner by postulating that carcinogenesis was composed of an *initiating process*, responsible for the conversion of normal into latent tumour cells, and a *promoting process*, whereby these latent tumour cells were made to develop into actual tumours.

A further development arose out of the investigations by Mottram (1944a, b, 1945).^{*} After confirming the epicarcinogenic action of croton oil for mouse-skin, Mottram investigated possible refinements in the technique, by testing the effect of croton oil in association with only a single application of benzo(a)pyrene. Thus he found possible, provided that the croton oil was applied several times *before*, as well as *after*, the single application of the carcinogen. From this (and by analogy with the response of ciliates to the action of carcinogens) he concluded that three factors were involved in the production of warts: (i) an initial *sensitizing factor*

(relatively non-specific, representing the conversion of quiescent into actively-dividing cells), (ii) a *specific cellular reaction* (the truly specific action brought about by a carcinogen, of which, under appropriate conditions, only a single application may suffice), and (iii) a *developing factor* (relatively non-specific, but responsible for the actual appearance of the visible tumours).

Since the results of Berenblum, of Rous and his associates, and of Mottram, obtained under somewhat different experimental conditions, and involving different terminologies, are closely related, it may be useful to try to correlate the results obtained, and to attempt a synthesis of their respective conclusions (see Table I).

TABLE I TERMINOLOGY OF RELATIONSHIPS IN EXPERIMENTAL CARCINOGENESIS

Stages of carcinogenesis	Nomenclature of		
	Rous et al	Mottram	Berenblum
Normal epithelium	—	—	—
Early (?) non-specific hyperplasia	—	Sensitizing factor	Precarcinogenic action
Specific preneoplastic hyperplasia	Initiating process	Specific cellular reaction	
Appearance of warts	Promoting process	Developing factor	Epicarcinogenic action
Progressive growth of warts		—	—
Conversion of warts into carcinomas	—	(A specific, independent process, not named)	Metacarcinogenic action
Progressive growth of malignant tumour	—	—	—

From the above schematic tabulation, it is seen that the sensitizing factor and the specific cellular reaction of Mottram are two stages of the precarcinogenic action of Berenblum, while the second (specific) stage of Mottram corresponds to the initiating process of Rous and collaborators. The latter is, however, a more precise concept, since it implies the development of latent tumour cells as definite (macroscopically invisible) foci, from which visible tumours may ultimately develop. The epicarcinogenic action, the developing factor, and the promoting process, again, deal essentially with the same phenomenon, namely, the relatively non-specific "precipitation" of a tumour at a site of preneoplastic hyperplasia. Of the three, the "promoting process" has, again, the most precise meaning, since it implies an action on macroscopically invisible, latent, tumour cells, instead of referring to an effect on the preneoplastic hyperplasia as a whole; it has, at the same time, a wider connotation, since it includes an influence on the progressive growth of the induced warts. Metacarcinogenic action is not included in the other schemes as a defined entity (though its existence is admitted or implied); and as regards the progressive growth of established malignant tumours, all are agreed that no extraneous influence is required for its maintenance.

^{*} These published results by Mottram carried out shortly before his death are based on relatively small numbers of animals. His interesting conclusions must, therefore, be accepted provisionally, awaiting their confirmation by others on a more adequate scale.

ANTI-CARCINOGENESIS

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Imperial Cancer Research Fund, London

A comprehensive definition of an anti-carcinogen would include any factor, intrinsic or extrinsic, which delays or prevents the emergence of malignant characters in any issue of any species of organism. Within a given species these opposing factors range from the natural biological background of the host that is, its genetic, endocrine and metabolic constitution to the many varieties of interference—dietetic, hormonal, chemical or physical—imposed in laboratory experiments.

The net result of any given experiment reflects the interplay of systemic and local responses and their mutual influences are difficult to disentangle. Genetically pure strains of mice may react uniformly to a single influence e.g. C3H mice to the "milk factor", but exhibit a wide variation of susceptibility to a chemical carcinogen.

Conscious of the diversity of these determinants of both carcinogenic and anti-carcinogenic action, workers in the field of anti-carcinogenesis pursue two objectives. Firstly, to elucidate possible rational modes of controlling the

development of cancer, with a preventive chemotherapy as a distant aim, and secondly, to glean information on the specific cell-changes which culminate in malignancy. Several hundred synthetic carcinogens of a wide variety of chemical types are now available and in no case is the mechanism of action understood, though in recent years a few clues have emerged.

INHIBITORS OF THE INDUCTION OF SKIN-CANCER

References to investigations up to 1944 can be found in several general reviews of cancer research (Cook Haslewood, Hewett, Hieger, Kennaway & Mayneord 1937, Cook & Kennaway, 1938, 1940, Dickens & Dodds, 1940, Burk & Winzler, 1944, Greenstein, 1945, Berenblum, 1944, Rusch 1944, Furth, 1944).

Berenblum (1944) has summarized the experimental work on chemical and physical agencies which retard, accelerate or leave unaffected the carcinogenic action of tar and polycyclic hydrocarbons. Variable degrees of inhibition have been produced by mustard gas and a few of its oxidized and substituted derivatives, cantharidine, CO_2 -snow, heptaldehyde, a phenolic fraction of tar, simple substances containing a labile halogen atom, *p*-thiocresol and strong sunlight. Some more-recently described inhibitors may be recorded here. Mottram (1945) showed that 3,4-benzpyrene was more active when painted on mouse-skin at midnight than at midday. The startling claims of Maisin (Maisin Pourbaix & Caeymaex 1938) that certain organic peroxides when injected at high dilution in mice skin painted with 3,4-benzpyrene, profoundly checked tumour induction have been

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These trends seem to represent a true advance in our understanding of the mechanism of carcinogenesis, the biological approach having succeeded in carrying the problem further than seemed possible by a purely morphological approach. Yet, recent work (Pullinger, 1940, 1941) does indicate specific histological changes in the skin in the early stages of treatment with carcinogens, while more recent cytological studies by Cowdry and his school (Cowdry, 1945), by Glucksmann

(1945), and others, suggest possibilities of further correlating morphological and biological aspects of carcinogenic action.

Finally, attention may be drawn to the practical implications (i.e. in relation to tumour development in man) arising from the demonstration that a number of relatively non-specific irritants are capable of "precipitating" a tumour in a tissue previously rendered preneoplastic, though incapable of inducing tumours on their own account.

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discounted by Belkin (1942), who repeated this work on a large scale and found no effect whatsoever on the normal genesis of induced and spontaneous tumours. Twort & Lyth (1944) used a colloidal preparation (active constituents, 30% tetrachlor ethylenum + 10% oleum pmi) and demonstrated a retarding effect on tumour induction by tar, 3 4-benzpyrene or shale-oil similar to that produced by their lanolin/olive-oil ointment. Crabtree (1940) chose a series of chloro-compounds graded with respect to the reactivity of their chlorine atoms and found a parallel effectiveness in opposing the carcinogenic action of 3 4-benzpyrene and 1 2 5 6-dibenzanthracene. A variety of acid chlorides, bromobenzene, unsaturated acids and the mercapturate-forming hydrocarbons naphthalene, anthracene and phenanthrene all proved potent inhibitors (Crabtree, 1941, 1944; 1945, 1946).

Lacassagne, Buu-Hoi & Rudali (1945) applied methylcholanthrene or 1 2 5 6-dibenzanthracene to the skins of mice, together with certain structurally related but non-carcinogenic compounds, and recorded a slowing of the rate of tumour induction by this device. Various aldehydes have been used in conjunction with carcinogens. Riley & Wallace (1941) and Riley & Pettigrew (1944) injected propionaldehyde or glyceraldehyde into mice and noted delayed sarcoma production, Carruthers (1940), guided by the work of Strong (1941), found pure heptaldehyde effective against skin-painted methylcholanthrene, Crabtree (1945), however, produced negligible inhibitions of 3 4-benzpyrene activity with a series of lower aliphatic aldehydes applied in a 4% concentration.

No basic standard of reference is available to permit an evaluation of the relative potencies of the various inhibitors listed above. Within a limited group of anti-carcinogens, e.g. the chloro-compounds used by Crabtree (1940), degrees of activity may be discerned when the experimental technique and mode of administration are standardized. Even on a qualitative basis it is difficult to conceive any property common to all the inhibitory agencies.

Berenblum (1944) has analyzed the available data in terms of a possible relationship between irritation and carcinogenesis, but finds this conception inadequate¹. In seeking for a more specific biochemical basis for anti-carcinogenic action, attempts have been made to correlate the power of checking tumour induction with that of damaging special metabolic processes. Berenblum, Kendal & Orr (1936) measured the effect of mustard gas and allied compounds on cell glycolysis, but found no simple relationship between this type of activity and anti-carcinogenic power. This may well have been due to technical difficulties arising from the varying solubilities and differing rates of hydrolysis of the substances tested. Crabtree (1941) found that a series of acid chlorides inhibited both cell glycolysis and tumour induction, but attributed the former to the liberation of HCl in the medium used for measurement, i.e. the glycolytic checking was non-specific and irreversible. Yet a group of non-hydrolyzing chlorine compounds, graded with respect to the lability of their chlorine atoms, showed anti-carcinogenic potencies in the same order as their powers of reversibly inhibiting glycolysis (Crabtree, 1940).

All these halogen compounds could act in another way, through condensation with SH-containing cell-components, thus impairing enzyme systems dependent on intact

SH-groups for their proper functioning. To test this possibility, other substances were chosen which could disturb S-metabolism by a chemical mechanism different from that which operates in glycolytic inhibitions. Bromobenzene has no effect on glycolysis *in vitro*, its halogen atom being relatively unreactive. When fed to animals it is metabolized, presumably in the liver, and excreted in the urine as a mercapturate. Applied to mouse-skin, a marked fall in the glutathione level of this tissue ensues, indicating that detoxication can take place in the skin itself. In conjunction with carcinogenic hydrocarbons it proved notably anti-carcinogenic (Crabtree, 1944).

Another class of chemical compounds, typified by the unsaturated maleic and citraconic acids, form addition-products with SH-containing molecules. These also disturbed the S-metabolism of mouse-skin by fixation of glutathione, and strongly opposed carcinogenic action (Crabtree, 1945). The antagonizing effect of heptaldehyde on skin-tumour induction by methylcholanthrene described by Carruthers (1940) could probably be attributed to a similar interference with S-metabolism, since aldehydes, under appropriate conditions, combine additively with SH-compounds, though the products are readily dissociable.

In investigations into the possible utilization of sulphur for the elimination of carcinogens, negative results were obtained with carcinogenic hydrocarbons when injected into rats by Elson, Goulden & Warren (1945) or painted on to mice by Crabtree (1946), though naphthalene, anthracene and phenanthrene, similarly applied, caused urinary mercapturate excretion. It was shown that each of these hydrocarbons, detoxicated in the skin, effectively checked the carcinogenic action of 3 4-benzpyrene and 1 2 5 6-dibenzanthracene (Crabtree, 1946). The inhibitions produced by substances structurally allied to the carcinogens (Lacassagne *et al.*, 1945) may operate through a similar mechanism, though the authors ascribed their findings to the possible competitive action between two substrates for the same enzyme.

These four classes of chemical substances would appear to possess only one common property when in contact with living cells, namely, that of checking S-metabolism. There is no direct evidence that sulphur plays any part in the detoxication of carcinogens, yet interference with S-metabolism tends to oppose the mechanism of carcinogenic action. Without referring to the unanalyzed complexities of the biochemistry of growth, these facts are most simply reconciled on the assumption that the carcinogenic hydrocarbons, probably in oxidized condition, become fixed to SH-containing cell-constituents, and that inhibitors of S-metabolism antagonize this process by preferential combination. It is tempting to speculate that disturbance of enzyme function through the formation of a carcinogen-enzyme complex could lead, by cellular adaptation, to the emergence of a new type of protein with autolytic properties. The hypothesis of Potter (1943) postulates that such an abnormal protein may arise in many ways and endow the cell with new characters which manifest themselves in uncontrolled growth.

The work of Weigert & Mottram (1946) on the metabolism of 3 4-benzpyrene, by the aid of fluorescence spectra, has shown that a series of intermediate compounds can be identified between the hydrocarbon itself and the final oxidized derivatives which are excreted. These intermediates contain radicals derived from unknown cell-constituents, and may conceivably represent the true carcinogens. The

¹ [See also article by Berenblum in this number (B 18 965) —ED.]

coupling may well involve SH groups and recalls the surmise of Wood & Fieser (1940), based on considerations of the special chemistry of 3,4-benzpyrene, that such a fixation may be an initial stage in the carcinogenic process

NUTRITIONAL FACTORS AS ANTI-CARCINOGENIC AGENTS

i Inhibitors of Liver-cancer Induction

Two of the most potent and widely investigated azo carcinogens are 4'-amino-2,3'-azotoluene and *N,N*-dimethyl-*p*-aminoazobenzene. They were discovered by the Japanese workers Sasaki & Yoshida (1935) and Kinoshita (1937), who also studied the influence of diet on hepatoma development, and isolated some of the products excreted by their molecular breakdown. The many confirmations and extensions of this work in Britain and USA are reviewed by Kirby (1945) and Morris (1945). These carcinogens, because of their simple chemistry and easy accessibility, seem particularly suitable for the investigation of the metabolic changes preceding malignant transformation.

They are more selective in their action than the carcinogenic hydrocarbons producing predominantly hepatomas and cholangiomas when fed to or injected into rats or mice. The tumours arise most readily in animals receiving a nutritionally incomplete diet, and the induction process can be hampered or prevented by a variety of dietary supplements. Cancer research has revealed nothing more arresting than the protective action of normal food-constituents on azo-carcinogenesis.

The exact nature of the metabolic deficiency which favours tumour induction cannot be simply formulated, since a wide range of dietary additions prove compensatory.¹ Substitution of rice, as first used by the Japanese, by other grains, e.g. wheat, rye or millet, lowers tumour incidence and extends the latent period. Inhibition has also been achieved by the incorporation of rice-bran yeast, liver, casein + riboflavin, casein + B-vitamins or dried whole milk in the basal cancer-promoting diet of rice and carrot or a synthetic equivalent. Three members of the B-group of vitamins have been shown to exert characteristic, but different, influences on azo-carcinogenesis. Riboflavin proved inhibitory, particularly when fed with additional protein (Miller, Miner, Rusch & Baumann, 1941; Miner, Miller, Baumann & Rusch, 1943). On the other hand, pyridoxine seems to act in the opposite way, hepatoma development is greatly retarded in its absence, but the incidence is augmented as increasing amounts are fed (Miner *et al.* 1943). Biotin supplements have been shown to stimulate tumour induction, and this effect can be annulled by avidin supplied by egg-white which inactivates the biotin (Du Vigneaud, Spangler, Burk, Kensler, Sugiura & Rhoads, 1942).

It is clear that the accumulated data are not amenable to simple interpretation. The multiple factors which act protectively seem to rule out the conception of a single and specific nutritional defect which fosters carcinogenic activity unless the many apparent abnormalities are regarded as secondary to the lowered functioning of one key enzymic

process. Such considerations have prompted experimental work on the identification of the metabolic end-products of the azo-dyes, and studies of their effects on isolated enzyme systems.

Aminophenols, *p*-diamines, and benzidine derivatives in free and acetylated form have been isolated. After further oxidation, the diamines derived from both carcinogenic and non-carcinogenic azo-dyes have been shown to inhibit the activity of a diphosphopyridine nucleotide system, carboxylase, urease and succinoxidase. Kirby's review (1945) of these phases of investigation emphasizes the complexity of the data, and makes it clear that no simple correlations have emerged between the various degrees of inhibitory power and the carcinogenic potency of the parent dyes. Potter (1942) on the assumption that quinone is the final oxidation product and the active agent in these inhibitions attributes their action to a fixation of SH containing enzymes.

ii The Anti-carcinogenic Effect of Caloric Restriction

A notable contribution in the field of anti-carcinogenesis is the demonstration that restricted caloric intake antagonizes the genesis of tumours. Tannenbaum (1945) has reviewed his comprehensive work on these lines and discussed its possible significance in the control of human cancer. Briefly, he has shown that the incidence of a wide range of spontaneous and artificially induced tumours of mice may be delayed or abolished when the available calories are limited in a diet deficient in carbohydrates but otherwise complete in all the recognized food essentials. The mice so fed are stunted in growth to a degree dependent on the restriction imposed.

Profound endocrine atrophy results from this limited dietary, and it is not surprising that, for example, mammary tumours fail to emerge. The whole animal appears to become markedly refractory to the most active carcinogens suggesting concomitant metabolic derangements of great complexity. The experiments emphasize the importance of the nutritional background of the host in determining cancer susceptibility. Indeed Tannenbaum (1940), moving from mouse to man, has analyzed the statistics of cancer mortality from the records of insurance companies and unfolded a correlation between overweight persons and their increased liability to cancer. He advocates a lower food-intake as a measure in the control of human cancer.

iii The Anti-carcinogenic Effect of Diets Deficient in Essential Amino-acids

White (1944) surveys work on the lowered incidence of mammary tumours in mice resulting from inadequate amounts of the essential amino-acids cystine and lysine in the diet. Here the inhibitory action is clearly indirect, since the abnormal diet initiates a progressive suppression of ovarian function and mammary tissue fails to proliferate.

It is evident that the time is not ripe for comprehensive generalizations on the mechanisms of anti-carcinogenesis as would be anticipated from our limited understanding of carcinogenesis itself.

¹ See also article by J. W. Orr in this number (*BMB* 975).—ED.]

THE INFLUENCE OF THE SOLVENT ON THE CARCINOGENIC RESPONSE

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The fact is now well recognized that the incidence of tumours, following the injection of a solution of a carcinogenic compound into animals, is greatly dependent on the nature of the solvent. Before the description of this phenomenon, it is desirable to indicate briefly why it has seemed to be worthy of detailed study. Any type of agent which is able to exert a controlling influence upon carcinogenesis is obviously of interest, not only because the possibility exists that the investigation of such agents may eventually lead to a more generalized control of some forms of cancer, but more particularly because such control may reasonably be expected to shed light on the most obscure stage of the action of chemical and other carcinogens, namely the mechanism of the primary induction of the carcinogenic change.

In spite of the vast range of chemical carcinogens of known constitution now available, numbering over 200, there is as yet no clear common property which they all possess and which might be considered as initiating the process of

carcinogenesis. On the contrary, the available carcinogens include, besides the well-known polycyclic hydrocarbons, substances such as urethane, carbon tetrachloride, sugar solutions, and even bakelite discs (Turner, 1941), quite apart from viruses and such purely physical agents as ultra violet and short-wave radiation, heat and cold. It has even been questioned if we have not too many carcinogenic agents, rather than any real understanding of how any single one of them acts.

The reviews of Crabtree¹ and Berenblum² have already indicated how the study of control of the action of carcinogens may provide a hopeful mode of approach to this outstanding problem of the primary induction of tumours. Among such agents, the solvents are particularly worthy of study, because the types of solvent which are quite active in this respect include naturally-occurring fats and lipids, substances which have usually been regarded as more or less inert, though indispensable components of all tissues, these substances not being characterized by any violent reactivity in the ordinary chemical sense.

In this respect, therefore, solvents appear to be in a different category from the reactive halogen-substituted compounds studied particularly by Berenblum (1929, 1931, 1935) and Crabtree (1941, 1944), the unsaturated dicarboxylic acids (Crabtree, 1945), or the compounds of sulphur such as the sulphhydryl-containing tissue amino-acids, believed to be concerned in the action of these compounds. In fact, this lack of chemical reactivity raises the question of whether the solvents depend on physical or chemical characteristics for their effects, evidence of the importance of minor components, tending to support a predominantly chemical explanation, will be discussed later. This is closely connected with the effect of the solvent upon the rate of elimination of the carcinogen from the animal body, which has now been measured systematically in a selected series of solvents, the

¹ [See (BMB 966) in this number—Ed.]

² [See (BMB 965) in this number—Ed.]

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results leave no doubt that a very wide variation in the rate of elimination occurs according to the particular solvent used and this in turn may be reflected in the suppression or augmentation of carcinogenic power of the hydrocarbon although it is only under otherwise highly favourable circumstances that this property is capable of providing a simple explanation of the solvent effect

From the immediate practical point of view, it is also important that these properties of various solvents should be more clearly understood, so as to make effective any comparison of the activity of various carcinogens. For the purposes of testing such substances, a wide variety of solvents has been used by various workers and their results are therefore not readily comparable and may even be misleading without such information

Mode of Administration of Carcinogen

In the following account only the results of experiments in which carcinogenic hydrocarbons were injected subcutaneously into the animal will be considered. The effect of solvents on the production of skin-tumours is discussed elsewhere in this volume, it is however, interesting to note here that there may be profound differences in the action of any one solvent according to whether it is applied externally or by injection. For example, Morton & Mider (1940) found that whereas a fatty extract of mouse carcasses inhibited carcinogenesis when used as a solvent for the subcutaneous injection of 3 4-benzpyrene into mice, a similar extract applied to the skin of mice just before they were painted with a benzene solution of the carcinogen yielded an increased number of tumours. Watson (1935) had previously described in rats a similar effect which he observed with mixtures of pinene tar and rat-tissue extracts. Baumann and co-workers (Baumann, Rusch, Kline & Jacob, 1940) found that cholesterol when dissolved in cottonseed oil (though not in benzene), definitely stimulated the rate of tumour production resulting from the painting of benzpyrene on the ears of mice. On the other hand, painting a benzpyrene solution in extract of mouse carcasses was found by Morton & Mider (1940) to give fewer skin-tumours than a similar solution in benzene.

By restricting the present discussion to subcutaneous administration, a good deal of confusion will thus be avoided, but the special advantage possessed by subcutaneous administration lies in the fact that it is the only feasible method which permits accurate quantitative analyses of the amounts of carcinogen present at any time after the injection as well as the administration of an accurately-measured dose

Choice of Dose of Carcinogen for Testing Pro- and Anti-carcinogenic Effects

Many of the earlier workers used very large doses of carcinogen in an endeavour to ensure a high incidence of tumours but this procedure is quite unsuited for the demonstration of pro- or anti-carcinogenic effects since these are liable to be completely masked by the excessive carcinogenic activity. This fact clearly recognized by Sall & Shear (1940) led these authors to recommend doses of the order of 0.1 mg. of 3 4-benzpyrene or 1 2 5 6-dibenzanthracene as a suitable amount for subcutaneous injection into the sensitive

FIG 1

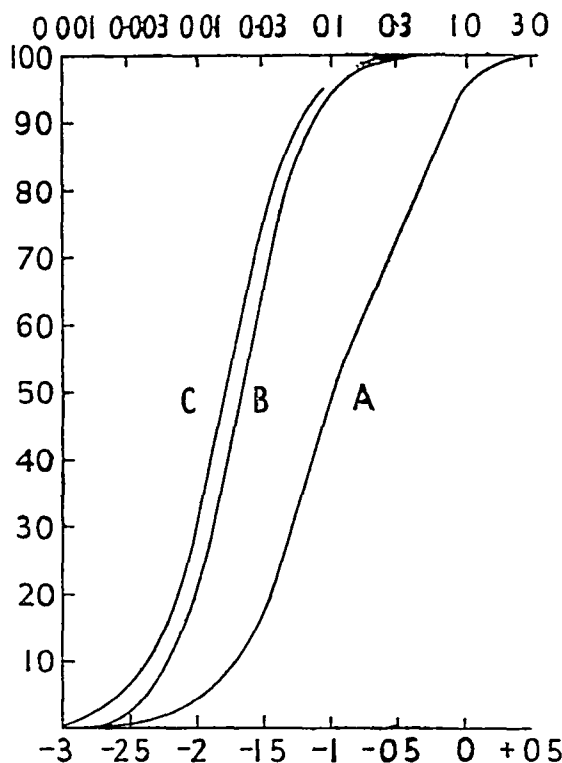


Fig 1 Incidence of local tumours in relationship to dosage of carcinogen. Data of Bryan & Shmkin (1943). Subcutaneous injection into Strain C3H mice of solutions in 0.25 ml. triacpryllin —

A = 3 4-benzpyrene

B = methylcholanthrene

C = 1 2 5 6-dibenzanthracene

Dosage of carcinogen as milligrams (upper abscissae) or as log milligrams (lower abscissae). Ordinates incidence of tumours (%)

(C3H) strain of mice used by them, for the still more active methylcholanthrene, the dose would have to be reduced to about 0.02 mg. The mice used by the writer give about a 50% cancerous response to doses of 0.3 mg. of 3 4-benzpyrene injected subcutaneously in 0.3 ml. of a "neutral" solvent, a "neutral" solvent here implies one that neither promotes nor retards carcinogenesis. This is therefore a convenient dose for tests with these particular mice. Fig. 1 adapted from the paper of Bryan & Shmkin (1943) shows the relationship between dose and tumour incidence observed by them.

The relationship of log dose to tumour incidence plotted on a scale of probability units approximates to a straight line or $y = 4.97 + 1.75(x + 1.01)$, where y = the calculated probit value and x is dose of 3 4-benzpyrene in log mg. Doses between about 0.05 and 0.3 mg. of benzpyrene fall within the useful range for tests of this kind. All experiments (on mice) with much larger or smaller doses are of little value for the present purpose.

Solvents which lead to a Relatively High Incidence of Tumours

For convenience we may distinguish between those solvents which appear to inhibit carcinogenesis and those which do not, although the distinction is by no means always definite, and the same solvent may give variable results at the hands of different workers, for reasons as yet mostly undefined.

Solvents hitherto described as yielding a high incidence of tumours even when they have been used for relatively small doses of carcinogen, include sesame oil (Strong & Smith, 1939), arachis oil (Athias & Furtado-Dias, 1938), olive oil (Peacock & Beck, 1938), paraffin (Dunning, Curtis & Bullock, 1936), several synthetic glycerides (Shimkin & Andervont, 1940), benzene (Murphy & Sturm, 1941), and some samples of lard (Andervont & Lorenz, 1937). Cholesterol in the presence of sufficient carcinogen also probably belongs to this group (Shear & Lorenz, 1939, Shear & Ilfeld, 1940). Many of these solvents are mixtures of variable composition, and in the case of lard (Shimkin & Andervont, 1940) the effect on carcinogenesis has been shown to vary from batch to batch. Some possible reasons for this will be suggested later.

Solvents which Prevent, Diminish, or Delay Carcinogenesis

Certain solvents, mostly complex mixtures, have previously been shown to exert an apparently anti-carcinogenic effect. Watson (1935) found that pinene tar mixed with rat-tissue extract gave rise to no tumours on subcutaneous injection into rats, but mixed with paraffin wax it produced sarcoma in 3 of 12 rats. Peacock (1935) had independently reported striking differences in the carcinogenic activity of 1,2,5,6-dibenzanthracene injected intramuscularly into fowls with lard, half the animals developed tumours, with "egg-yolk fat" or "chicken fat," no tumours appeared. More recently, Murphy & Sturm (1941) have found in similar experiments that whereas 96% of tumours were obtained by benzene solutions, the local carcinogenesis with lard (30% of tumours) and chicken fat (10%) was much lower, on the other hand, distant tumours and other indications of dispersal (liver damage and leukosis) were observed only with the 2 latter solvents.

Results similar to those of Peacock (1935) were reported for mice by Peacock & Beck (1938), who used in this series of experiments 0.5 to 1 mg of 3,4-benzpyrene given subcutaneously. Whereas the powdered solid substance, or its solution in ethyl ether or in "mouse-fat" produced only a few tumours, carcinogenic activity was pronounced when the solvent was olive oil, "mouse lipoids containing fats and sterols", or a mixture of olive oil and paraffin. In this second group, "the solvents used tended to be retained at the site of injection, and also to render the absorption of benzpyrene slower" (Peacock & Beck, 1938). The solvents of the former group were regarded as producing an effect tantamount to solution in the mouse's own fat.

Morton & Mider (1939) obtained only 1 tumour in 44 mice which had received subcutaneously 0.25 mg of 3,4-benzpyrene dissolved in a light petroleum extract of mouse carcasses, while the same amount of hydrocarbon dissolved in sesame oil produced 36 tumours in 46 mice.

The striking results of Peacock & Beck and Morton & Mider could not be confirmed by Oberling, Guerin & Sannie

(1939), Oberling, Guerin & Guerin (1939), or Shimkin & Andervont (1940). These authors found no effect of homologous fat, from the rat and mouse respectively, on tumour production by carcinogenic hydrocarbons. Shimkin & Andervont also obtained no special effect when liver fat, brain fat, abdominal fat, chest fat, or fat from the rest of the body of the mouse was used as solvent.

Some of the anomalous results can probably be excluded from consideration merely on the ground that the doses of carcinogen used were too high, as has been discussed above. Thus Oberling and his associates (1939) and Shimkin & Andervont (1940) both used very high doses, the former 25-75 mg of benzpyrene injected into rats, and the latter 0.5 mg or more of the highly active carcinogen methyl cholanthrene into mice. Such doses are already sufficient to give a maximum carcinogenic response and are not therefore suitable for revealing an anticarcinogenic action, unless very powerful, nor could they be used to detect any procarcinogenic effect.

Use of Homologous Solvents

In view of these inconsistencies, it was decided to investigate the relation of solvent to carcinogenesis in some detail (Dickens & Weil-Malherbe, 1942). The first points to be cleared up were (a) confirmation of the anti-carcinogenic effect of homologous fat, i.e., of fat obtained from the same species of animal, on which the experiments of Peacock & Beck, and of Morton & Mider, cited above, had already focussed attention. The work of both groups of authors stressed the possible importance of the fact that fat from the same species might be less "foreign" to the animals, and so produce less local reaction to the injection, a point to which Peacock & Beck were the first to attach particular importance. In their view, such homologous solvents tended to be retained at the site of injection, and also to render the absorption of benzpyrene slower. This impression was based on visual examination of the animals, the presence of fluorescence in the ultra-violet beam being taken as a rough measure of the persistence of the hydrocarbon at the injection site.

These observations therefore needed to be reinforced by (b) the use of body-fat obtained from a quite different species, and (c) exact measurement of the rate of elimination of the carcinogen, visual observation by qualitative methods being, in our experience, a very insecure guide to the fate of the injected benzpyrene. Step (c) involved the elaboration of a rapid and accurate method for the estimation of the carcinogen in animal tissues, which was successfully achieved (Weil-Malherbe, 1944a, b) by a combination of chromatographic purification of the benzpyrene extracted from the tissues, with its fluorimetric estimation in the purified extracts.

No difficulty was experienced in confirming the inhibitory effect on tumour incidence when a solution of benzpyrene in mouse fat was compared with the same amount of benzpyrene dissolved in sesame or arachis oil, and it was found that a considerable degree of purification of the crude extract of mouse carcasses could be achieved without loss of this property. A freshly prepared "neutral fat fraction", which had been partially freed from phospholipins by precipitation with acetone, still showed an inhibitory effect on benzpyrene carcinogenesis (see Fig. 2). This preparation (mouse fat A) contained about 2% cholesterol and 1.5% phospholipins (Dickens & Weil-Malherbe 1942).

FIG 2

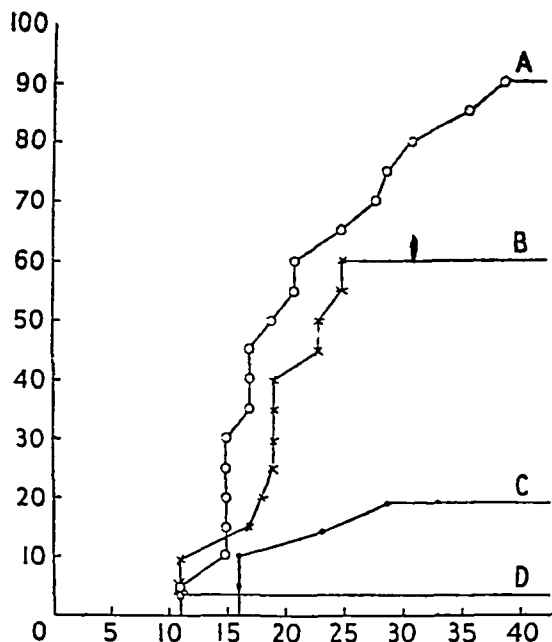


Fig 2. Incidence of local tumours following the injection into mixed-strain mice of 0.3 mg 3,4-benzpyrene dissolved in 0.3 ml of following —

- A = sesame oil
- B = arachis oil
- C = mouse fat, not highly purified (Sample A)
- D = ox brain lipids

Abscissae weeks after injection,
Ordinates Incidence of tumours (%)

(Dickens & Weil-Malherbe 1942)

That this inhibition was not limited to homologous fat was shown by the fact that it was possible to prepare from ox-brain a mixture, containing fats, phospholipins, and cholesterol, which also led to the occurrence in the mice of fewer tumours than the control solutions of benzpyrene in sesame and arachis oils (Dickens & Weil-Malherbe, 1942, see Fig. 2). Out of an effective total of 29 mice receiving subcutaneous implants of pellets of 0.3 mg ox-brain lipids containing 0.3 mg. benzpyrene, only one mouse developed a tumour, whereas among an effective total of 40 mice injected with the same dose in vegetable oils, 30 animals developed malignant tumours.

Differences between Animal and Vegetable Fats

The fact that the inhibitory effects observed were shown by fats and lipids from animal sources, and were absent from the vegetable oils tested suggested that they might be connected with one or more components present in the animal fats but absent or present in insufficient amount, in the vegetable oils. Among the components notably present in animal fats are phospholipins and highly unsaturated fats, e.g., glycerides of arachidonic and clupanodonic acids, and these were therefore tested for anticarcinogenic activity

(It is not implied that there may not be other components concerned, particularly antioxidants other than phospholipins a possibility discussed below.) Accordingly purified lecithin and cephalin were prepared from ox-brain, made into thick pastes with an equal weight of tricaprilyn and used as solvents for the standard dose of 0.3 mg benzpyrene. As an example of a fat unusually rich in polyethenoid unsaturated acids cod-liver oil was chosen. There was a notably lower incidence of tumours in the lecithin and cephalin groups of mice (9% to 11% of mice had local tumours) than in the control group which received tricaprilyn solution of benzpyrene (33% of tumours). On the other hand, the incidence in the cod-liver-oil group was substantially the same (37%) as in the tricaprilyn group. The only effect attributable to the use of cod-liver oil was a tendency to earlier tumours (Weil-Malherbe & Dickens 1944). The phospholipins however, even when considerably purified had an inhibitory effect on benzpyrene carcinogenesis, an observation that accorded well with the inhibitory action observed in our earlier experiments with the cruder brain lipids the latter material being also fairly rich in phospholipins.

The fact that the highly unsaturated fatty acids were not responsible for the inhibitory effect agrees with the correlation noticed by Leiter & Shear (1943) between the retardation of tumour induction and the degree of saturation of the long-chain fatty acids present in a triglyceride solvent, the abundance of unsaturated fatty acids in cod-liver oil may even have been responsible for the earlier appearance of tumours with this solvent in comparison with the fully saturated tricaprilyn. A special affinity of growing tumour tissue for highly unsaturated fatty acids is suggested by the observation of Smedley-McLean and co-workers (Smedley-McLean & Nunn 1941, Smedley-McLean & Hume, 1941) that these acids disappear from the subcutaneous tissues of rats bearing rapidly-growing transplanted tumours.

Further evidence supporting the relative unimportance of unsaturation in regard to the total incidence of neoplasms was provided by a comparison of unsaturated fats with the same fats after catalytic hydrogenation (Dickens & Weil-Malherbe, 1946). Hydrogenated cod-liver oil used as a solvent for benzpyrene, gave a slightly lower incidence of tumours and a longer induction period than the unhydrogenated solvent, though the difference in total incidence was not statistically significant. A sample of nearly pure neutral triglyceride prepared from dissected adipose tissue of the mouse was only slightly more procarcinogenic after hydrogenation than was the same fat in its natural unhydrogenated state. There was therefore no consistent correlation between degree of hydrogenation of the solvent and the carcinogenic activity, in any event the effect of hydrogenation on carcinogenesis was slight.

In these experiments careful measurements were made of the rates of elimination of the carcinogen from the body of the mouse. The rate was accelerated in the unsaturated fats, but after their hydrogenation the rate of elimination was slowed down to equal that observed with tricaprilyn. The latter solvent behaved as a truly "neutral" diluent, and did not affect the tumour incidence observed with solvents with which it was mixed. This point has been of practical use in diluting and liquefying solvents which would otherwise be too hard or too viscous for injection and in the later experiments tricaprilyn provided a reliable standard solvent for purposes of comparison.

The Nature of the Anticarcinogenic Factor in Crude Mouse Fat

In order to investigate this question, mouse fat was prepared which consisted mainly of the triglyceride fraction, admixed with some cholesterol (0.167%) but containing very little phospholipins (0.05%). This was done by dissecting out the adipose tissue before extracting it with acetone, previously we had followed other workers in extracting the whole mouse, a process which invariably yields a material containing much higher amounts of phospholipin, as well as more cholesterol

FIG 3

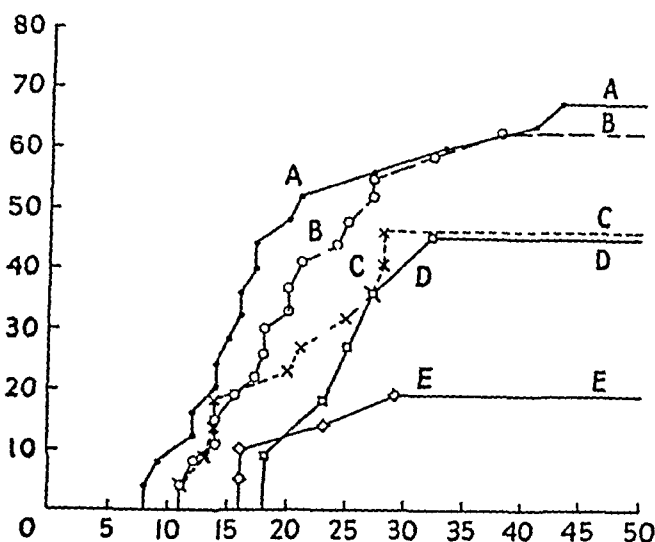


Fig 3 Incidence of local tumours Data as for Fig 2 Solvents used —
A = mouse fat, purified (Sample B) plus equal vol tricapyrylin
B = mouse fat, purified (Sample B), alone
C = tricapyrylin alone
D = mouse fat, not highly purified (Sample A), kept 3 years
E = mouse fat, not highly purified (Sample A), freshly prepared
Abscissae weeks after injection,
Ordinates incidence of tumours (%)

This purer mouse fat (preparation B, Fig 3) proved to have no inhibitory effect on carcinogenesis (Dickens & Weil-Malherbe, 1946). Moreover, the cruder mouse fat originally found to be anticarcinogenic (preparation A, Fig 3), after it had been kept at room temperature for 3 years was found to have lost its anticarcinogenic action (see Fig 3)

These experiments strongly suggested that an unstable component of the original mouse fat was concerned in its anticarcinogenic activity. Since the experiments described above did not support the view that unsaturated fatty acids were responsible, the most obvious component likely to be anticarcinogenic appeared to be the phospholipins, even though these were present to the extent of only about 1.5% in the original mouse fat (preparation A). The experiments of Weil-Malherbe & Dickens (1944) had shown that 50% solutions of phospholipins were inhibitory towards carcinogenesis, but it remained to be shown that much weaker solutions, of about the same concentration as that of phospholipins in the mouse fat, were also inhibitory. Since the mouse-fat preparations all contained some cholesterol, the effect of this component was also tested

Action of Dilute Solutions of Phospholipins and Cholesterol on Carcinogenesis and Elimination Rates

Fig 4 shows the incidence of neoplasms following the injection of solutions of benzpyrene in (a) pure tricapyrylin (b) 3% cholesterol in tricapyrylin, (c) tricapyrylin containing 1.5% brain cephalin and 1.5% brain lecithin (Weil-Malherbe & Dickens, 1946). The tumour incidence at 20 and 30 weeks was cholesterol series, 79% and 82%, tricapyrylin 38% and 46%, phospholipins 12% and 47%, respectively. The mean rates of elimination of benzpyrene from the animals are shown in Fig 5, from which it is clear that the rate is accelerated when the solvent contains cholesterol and inhibited in the phospholipin solution, as compared with tricapyrylin. The values of the elimination constants (k) shown on the curves (Fig 5) are calculated for a unimolecular type of equation, $k = -\frac{1}{t} \log \frac{A}{s}$, where t = time in days from injection of an amount A of benzpyrene, s = amount remaining. Statistical analysis showed that the values of k were significantly different in the different solvents ($P < 0.01$)

In these experiments, where considerable care was taken to equalize as far as possible all the variables other than the solvent, and also to compare only solvents of closely similar

FIG 4

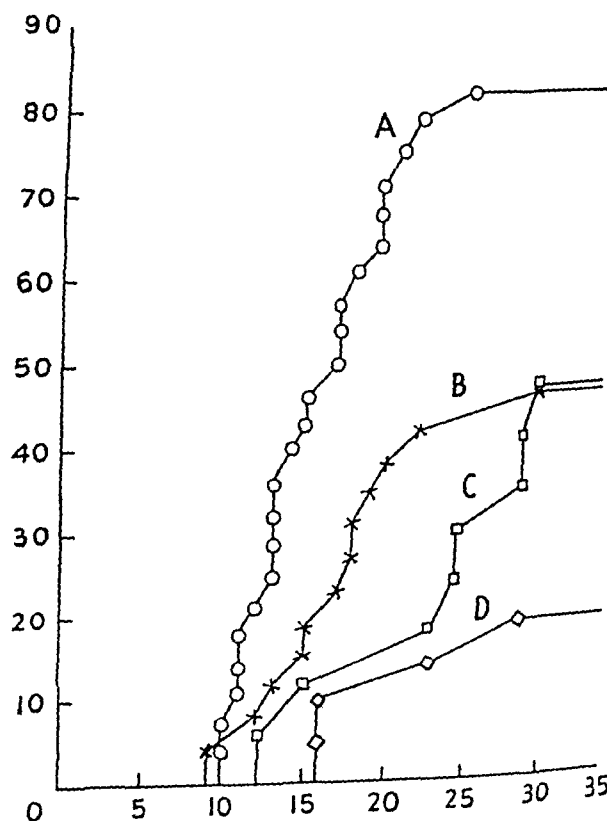


Fig 4 Incidence of local tumours after injection into Glaxo FF mice of 0.3 mg 3,4-benzpyrene in 0.3 ml of following solvents —
A = tricapyrylin containing 3% cholesterol
B = tricapyrylin alone
C = tricapyrylin containing 1.5% cephalin and 1.5% lecithin
D = fresh mouse fat (Sample A), for comparison
Abscissae weeks after injection,
Ordinates incidence of tumours (%)
(Dickens & Weil-Malherbe 1946)

FIG 5

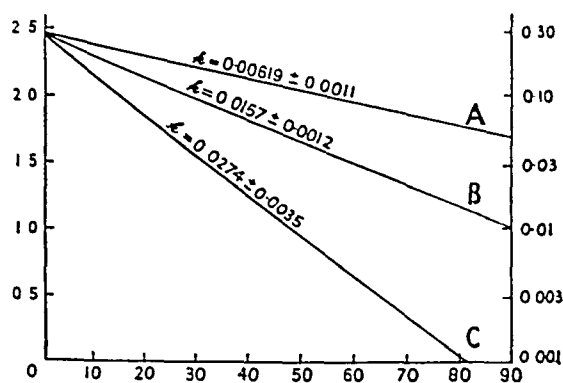


Fig 5 Mean elimination rates of 0.3 mg 3,4-benzpyrene after its subcutaneous injection into Glaxo FF mice. Solvents —
 A = tricaprylin containing 15% cephalin and 15% lecithin
 B = tricaprylin alone
 C = tricaprylin containing 3% cholesterol

The amounts remaining in the bodies of the mice are shown on the ordinates, left scale = log micrograms of benzpyrene, right scale = milligrams of benzpyrene. Abscissae days after injection. Mean values of the elimination constant (k , for definition see text), together with their standard errors, are shown on the curves

Weil-Malherbe & Dickens (1946)

physical properties, the surprising result was obtained that the more rapid elimination of benzpyrene was associated with the higher carcinogenic activity, and slower elimination with lower activity. It would be unwise to generalize from these findings too widely, but the results nevertheless clearly show the incorrectness of the view that rapidity of elimination of the carcinogen is necessarily what determines low carcinogenic activity in such cases. On the contrary, it is suggested that the results become explicable if the participation of the carcinogen in metabolic reactions is regarded as a *sine qua non* of its activity. Presumably such participation would take the form of oxidative conversion of the hydrocarbon to a metabolite, which may be primarily an unstable precursor (cf Weigert & Mottram, 1946a,b) of the phenolic compounds hitherto isolated in metabolic investigations of the fate of injected hydrocarbons (Chalmers & Peacock 1941, Berenblum & Schoental 1943).

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On this basis, the delayed elimination of benzpyrene observed by Weil-Malherbe & Dickens (1944, 1946) in the presence of phospholipins could perhaps be accounted for by the known antioxidant properties of these compounds. In a study of the *in vitro* oxidation of benzpyrene in the presence of autoxidizing dioxan, which acted here both as solvent and inducer of oxidation of benzpyrene it was found that phospholipins effectively inhibited the oxidation of the hydrocarbon (Dickens, 1946). Thus the antioxidant properties of the phospholipins might furnish a rational explanation of their anticarcinogenic action if only as a provisional working hypothesis. It is quite probable that this reaction would be enhanced by other antioxidants present in natural fats, which are known to be capable of synergistic action (cf Hickman, 1943), and of which some may be even more effective than the phospholipins. On the other hand it must be admitted that no such explanation is at present available for the procarcinogenic action of cholesterol, which was not found to accelerate the *in vitro* oxidation of benzpyrene, in experiments similar to those mentioned above.

An important corollary of the above hypothesis would be that the true carcinogen is not the hydrocarbon itself—which may lie in contact with tissues for months, in the presence of a suitable inhibitor, without producing cancer—but that the active metabolism of the carcinogen is a necessary condition for its carcinogenic activity. If this is so, a metabolite, presumably produced by oxidative metabolism from the hydrocarbon, should probably be regarded as the true carcinogenic substance.

It is not unlikely that further extension of this work may greatly modify these preliminary suggestions. A major problem is to distinguish between physical and chemical influences on elimination rates. It is evident that merely the rapid excretion of a carcinogen due, for example, to the presence of a solubilizing agent, would not, on the above theory, be expected to augment carcinogenesis. Some confirmation of this has been obtained by Weil-Malherbe (1946c), who injected mice with the true aqueous solutions of benzpyrene obtainable by the use of purine derivatives as solubilizers (Weil-Malherbe, 1946a, b). Under such conditions, the rate of elimination of the water-soluble benzpyrene was extremely rapid, about twenty times that observed in tricaprylin, and only a very low incidence of cancer resulted. As a provisional hypothesis, therefore, it is suggested that those inhibitory solvents which retard elimination, inhibit chemically the oxidation of the hydrocarbon, and owe to this property their anticarcinogenic action.

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Continued at foot of page 354

METABOLISM OF CARCINOGENIC COMPOUNDS

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Although aromatic hydrocarbons are insoluble in water, they have definite biological effects. Benzene has a destructive action on myeloid tissue, naphthalene causes degeneration of the crystalline lens in rabbits (Adams, 1930), and many of the more complex polycyclic hydrocarbons are carcinogenic and inhibit growth. These biological actions may be due to the hydrocarbons themselves but, in view of their insolubility in water, it is possible that the action occurs in the lipid phase or oil-water interface of tissues, or that the hydrocarbons are converted into water-soluble compounds which are the proximate causes of the biological effects.

The metabolism of a drug may lead to activation or detoxication. The metabolism of prontosil results in the formation of sulphanilamide, which is a bacteriostatic compound. The further metabolism of sulphanilamide to acetyl sulphanilamide is a detoxication or inactivation-process. The hydrocarbons anthracene and the carcinogenic 1,2,5,6-dibenzanthracene are metabolized to different products by rats and rabbits. Now whereas the injection of 1,2,5,6-dibenzanthracene into rats generally leads to tumour formation at the site of injection, such treatment rarely (if ever) produces this effect in rabbits. The two tumours in rabbits described by Haagensen & Krehbiel (1936) were induced when the 1,2,5,6-dibenzanthracene was injected in liquid paraffin at 80°C. The combined action of heat and carcinogenic agent may possibly produce an effect different from that of the carcinogen alone, and these two tumours are the only ones described as occurring at the site of injection out of several hundred rabbits which have been injected.

It is possible that the difference in response of the two species is due to difference in metabolism. The tissues of rats may transform the hydrocarbons into carcinogenic substances, while rabbit tissues convert 1,2,5,6-dibenzanthracene into non-carcinogenic derivatives. Although this hypothesis fits the facts, much work still requires to be done before it becomes more than a hypothesis. If it could be substantiated, we should be nearer to understanding the nature of the process of carcinogenesis. If metabolic changes are involved in the whole process, then it might be possible to prevent the carcinogenesis by changing the metabolism by dietetic or other means.

Benzene, Naphthalene and Chrysene

The conversion of benzene to phenol in men and dogs was first shown by Schultzen & Naunyn (1867). Benzene is also converted to catechol and hydroquinone, while a small amount is converted to muconic acid by opening of the benzene ring. It is remarkable that the muconic acid excreted by rabbits is of the *trans-trans* form, and that the *cis-cis* form is apparently converted into the *trans-trans* form on standing as a solution in urine from a rabbit dosed with benzene (Drummond & Finar, 1938). Benzene is also excreted as phenyl mercapturic acid, which has been isolated from the urine of rats dosed with benzene or phenyl *L*-cysteine (Zbarsky & Young, 1943).

The fate of naphthalene in the animal body has also been studied for a long time. Baumann & Herter (1877) found that the urine of dogs fed with naphthalene contained a soluble compound which gave naphthalene on treatment with acid. This soluble naphthalene precursor has still not been isolated. Lesnik (1888) isolated α -naphtholglycuronic acid from the urine of dogs dosed with naphthalene, and Bourne & Young (1934) isolated *L*- α -naphthylmercapturic acid from the urine of rabbits dosed with naphthalene, and confirmed its structure by synthesis. These results show that, in the metabolism of naphthalene, α -substitution occurs and derivatives of α -naphthol (I) are found.¹

The metabolism of chrysene has been studied by Berenblum & Schoental (1945), who injected the substance into rats and examined the excreta. By the use of chromatographic

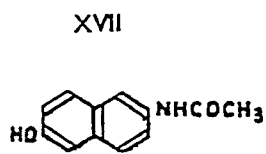
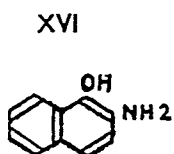
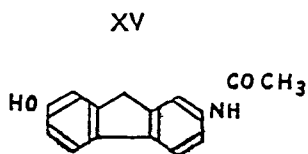
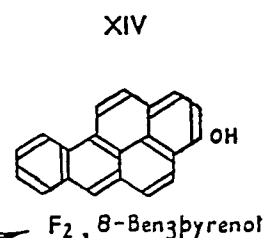
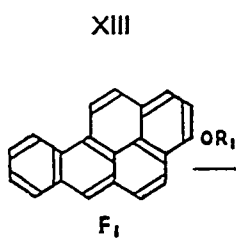
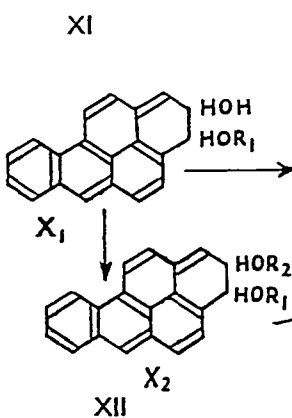
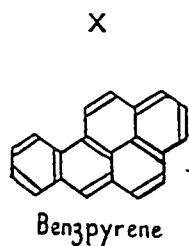
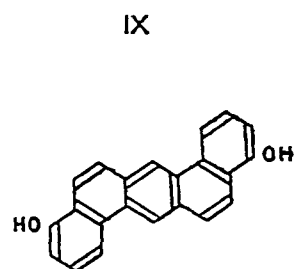
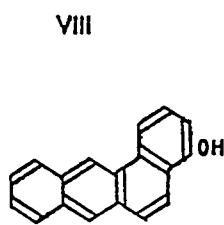
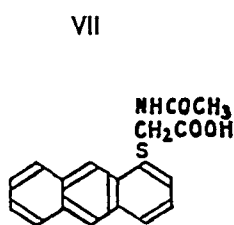
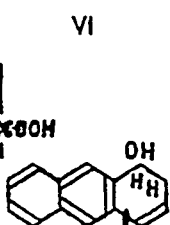
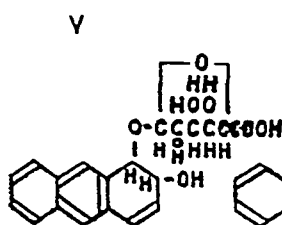
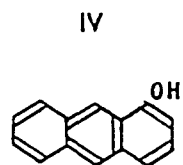
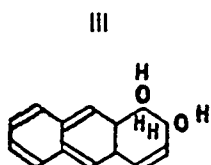
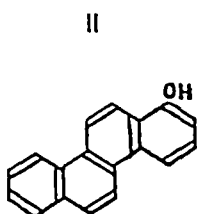
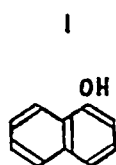
¹ Young (1946) has now isolated an optically active 1,2-dihydroxy-1,2-dihydronaphthalene from the urine of rats dosed with naphthalene. This diol which gives a naphthol on acid hydrolysis is probably the precursor of the α -naphthol which had previously been isolated from urine.

INFLUENCE OF SOLVENT ON CARCINOGENIC RESPONSE

Continued from page 353

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analysis, a phenol was isolated which was converted into a methoxychrysene. This methoxychrysene was shown to be identical with 3-methoxychrysene, which had been synthesized by Cook & Schoental (1945). The chief metabolic product is therefore 3-hydroxychrysene (II). Substitution has not taken place in the chemically reactive 2-position, but in the less active 3-position, which corresponds to the α -position of a substituted naphthalene nucleus.

Anthracene

The study of the metabolism of anthracene has revealed peculiar differences between species. When anthracene is fed to or injected into rats or rabbits, several water-soluble derivatives are excreted in the urine. The most abundant metabolites are the "diols", or 1,2-dihydroxy-1,2-dihydroanthracenes (III) and their monoglycuronides (Boyland & Levi, 1935, 1936a). The physical properties of the compounds and derivatives obtained from the two species are given in Table I.

TABLE I. PHYSICAL PROPERTIES OF ANTHRACENE DERIVATIVES OBTAINED FROM URINE OF RATS AND RABBITS

		Property of compound derived from	
		Rat urine	Rabbit urine
Melting point of 1,2-dihydroanthracene	2-dihydroxy-1,2-dihydroanthracene	160-161°	184°
[α] _D in dioxan of 1,2-dihydroanthracene	2-dihydroxy-1,2-dihydroanthracene	-80°	0°
Melting point of 1,2-dihydroanthracene	2-diacetoxy-1,2-dihydroanthracene	122 and 147° (dimorphic)	122°
[α] _D in dioxan of 1,2-dihydroanthracene	2-diacetoxy-1,2-dihydroanthracene	240°	0°
[α] _D in dioxan of 1,2-dihydroanthracene glycuronide	2-dihydroxy-1,2-dihydroanthracene glycuronide	-114°	+197°

Boyland & Shoppee (in press) have made a further examination of these diols and conclude that both compounds have the *cis* structure, and that the rabbit diol is an optically inactive mixture of the *d* and *l* forms. Both types of dihydroxydihydroanthracene are easily dehydrated to give the phenolic α -anthrol or 1-hydroxyanthracene (IV). The properties of the glycuronides of the dihydroxydihydroanthracenes (V) are also different, although these also lose water and give α -anthrol glycuronic acid on treatment with acid.

These experiments established the fact that a hydrocarbon can be attacked in the animal body in such a way that the elements of hydrogen peroxide are added to yield neutral water-soluble compounds. This reaction has been called "perhydroxylation" (Fieser, 1941), and is of particular interest in view of the stereochemical differences found in the two species which were examined.

The urine of both rats and rabbits which had been dosed with anthracene gave free anthracene when heated with acid. The actual anthracene precursor has still not been isolated but, by analogy with the dihydroxy-dihydroanthracene results, it seems possible that it is a hydroxy-dihydroanthracene (VI) which, on treatment with acid, loses the elements of water. Both rats and rabbits also excrete *l*-anthrylmercapturic acid (VII) (Boyland & Levi, 1936b), but in this case the same product is excreted by both species.

Quick (1937) has suggested that "the union of cysteine with the hydrocarbon might be the first and only step available to the organism for attacking the unsubstituted aromatic ring and that as a further reaction the mercapturic acid is

replaced by a hydroxyl group". This hypothesis still remains unproved, but the fact that phenylcysteine is excreted as phenylmercapturic acid indicates that the linkage between cysteine and an aromatic compound is not readily altered in the body.

An interesting point about anthracene metabolism is that the reacting groups enter the molecule on carbon atoms which are not particularly reactive. In most chemical reactions the meso- or 9- and 10-positions are usually attacked, whereas in animals substitution takes place on the 1- or 2-carbon atoms of the side rings. This type of action, in which hydroxylation occurs at centres of secondary reactivity, has also been found in metabolism of more complex hydrocarbons. It is possible that the hydrocarbon is combined with an enzyme or with some other tissue constituent (such as ascorbic acid, cf. Warren, 1943) or a purine (Weil-Malherbe, 1946) through the 9- and 10-carbon atoms, so that the side rings are the only rings open to attack. The carcinogenic activity of 9,10-dimethyl-1,2-benzanthracene and of 9,10-dimethylanthracene shows that the unsubstituted meso-positions are not essential for carcinogenic action. On the contrary, substitution of these centres of chemical activity by methyl groups increases the carcinogenic activity.

1,2-Benzanthracene and 9,10-Dimethyl-1,2-Benzanthracene

Anthracene is not carcinogenic, but 9,10-dimethyl-1,2-benzanthracene and 1,2,5,6-dibenzanthracene are carcinogenic when tested by the usual methods. 1,2-Benzanthracene is a border-line substance with slight carcinogenic activity. Berenblum & Schoental (1943b), with Holiday (1943), examined the faeces of mice and rats which had been injected with 1,2-benzanthracene. By chromatographic analysis on alumina they isolated a fluorescent phenol. The phenol was converted into the more stable methoxy-compound which was compared in chromatographic behaviour, fluorescence spectra and absorption spectra with 9,10-dimethoxy-1,2-benzanthracene and with 4'-methoxy-1,2-benzanthracene. The evidence obtained suggests that 1,2-benzanthracene is converted into 4'-hydroxy-1,2-benzanthracene (VIII) by rats and mice.

Dickens & Weil-Malherbe (1945) have obtained spectrographic evidence that 9,10-dimethyl-1,2-benzanthracene is converted to the 4'-hydroxy-9,10-dimethyl-1,2-benzanthracene by rats. Thus the chemical processes in the metabolism of the carcinogenic 9,10-dimethyl-1,2-benzanthracene and of the doubtful carcinogen 1,2-benzanthracene are similar.

1,2,5,6-Dibenzanthracene

The changes undergone by 1,2,5,6-dibenzanthracene in the body are of particular interest, as this substance was the first known carcinogen of definite structure and is still the most potent from the quantitative aspect when injected into mice (Bryan & Shumkin, 1943).

A metabolic product of 1,2,5,6-dibenzanthracene was first isolated from rabbit urine by Levi & Boyland (1937), and later characterized by Boyland, Levi, Mawson & Roe (1941) and Dobriner, Rhoads & Lavin (1942). Dobriner and his co-workers studied the metabolism in different species and recovered 1,2,5,6-dibenzanthracene from both urine and faeces of rats, mice and rabbits following subcutaneous injection of the hydrocarbon. They also obtained evidence indicating that a compound with phenolic properties was

excreted by rats and mice, and that a different dihydroxy-1 2 5 6-dibenzanthracene was excreted by rabbits. The substance isolated from the urine of rats and mice was shown to be identical with 4'-8'-dihydroxy-1 2 5 6-dibenzanthracene (IX) synthesized by Cason & Fieser (1940). The structure of the phenolic derivative of 1 2 5 6-dibenzanthracene which has been isolated from rabbit urine is still not settled, but it yields a quinone on oxidation which is not identical with the 3 7-dihydroxy-1 2 5 6-dibenzanthraquinone which has been synthesized by Cason & Fieser (1941). Jones (1942) used spectrographic methods and could detect no hydroxylated derivatives in the tissues. He found that much more unchanged 1 2 5 6-dibenzanthracene than dihydroxy-1 2 5 6-dibenzanthracene appeared to be excreted both in the faeces and in the urine.

Both the phenolic derivatives of dibenzanthracene which have been isolated have been reported as being non-carcinogenic, the rabbit derivative having been tested in mice both by Boyland *et al.* (1941) and Dobriner *et al.* (1942), and the rat derivative (as synthetic 4'-8'-dihydroxy-dibenzanthracene) by Dunlap & Warren (1941). These results are in agreement with the general rule that introduction of phenolic groups into the carcinogenic hydrocarbon molecule results in loss of carcinogenic activity. It is possible that these dihydroxy-1 2 5 6-dibenzanthracenes which have been isolated are formed either by natural processes of metabolism or artificially during extraction from non-phenolic tetrahydroxy-tetrahydro-1 2 5 6-dibenzanthracenes. Such tetrahydroxy-tetrahydro-derivatives, analogous to the anthracene metabolism products, are purely hypothetical, but it is possible that such compounds formed in the tissues might be carcinogenic. The testing of this hypothesis must wait until such compounds are available.

3. 4-Benzpyrene

3 4-Benzpyrene is one of the more rapidly acting carcinogenic hydrocarbons, and the main compound responsible for the carcinogenic activity of coal-tar. As most benzpyrene derivatives have intense and typical fluorescence spectra their presence can easily be traced in the excreta and tissues of animals. The application of benzpyrene is followed by excretion of only small amounts of metabolites in the urine, on the other hand, relatively large amounts are excreted in the faeces. As only minute amounts of unchanged hydrocarbon (Chalmers & Kirby, 1940; Berenblum & Schoental, 1942) are found in the excreta, it is possible that the animal eliminates the foreign compound mainly by metabolic processes.

Extracts from the pooled faeces in suitable solvents can be separated by fluorescence chromatography into various fractions. The most conspicuous fraction forms a zone with a yellow fluorescence, but in solution it fluoresces brilliantly blue. Chalmers & Crowfoot (1941) isolated minute amounts of crystals from this fraction, which, according to crystallographic analysis appeared to be a benzpyrene-monophenol. That this phenol was 8-benzpyrenol (XIV) was established by Berenblum and co-workers (Berenblum & Schoental, 1943a; Berenblum, Crowfoot, Holiday & Schoental, 1943), who made use of the fact that unstable phenols are easily oxidized to quinones, and that they can be transformed into more stable methoxy-derivatives. The structure of benzpyrene quinones has been established by synthesis (Vollmann, Becker, Corell & Streeck, 1937; Fieser & Hershberg (1939)

synthesized 5-benzpyrenol, and Cook & Schoental (in press) have prepared 10-benzpyrenol.

Recent work of Berenblum, Schoental, Holiday & Jope (1946) has shown that both rats and rabbits excrete 8- and 10-benzpyrenols, which can be oxidized to 5 8- and 5 10-benzpyrenequinones respectively. Rats excrete relatively less 10-benzpyrenol in relation to the 8- isomer than do rabbits. The species differences are therefore quantitative rather than qualitative, in so far as the metabolic end-products are concerned. The metabolic production of phenols from benzpyrene fits the rule established with the other hydrocarbons, as the molecule is not attacked at the 5-position which is chemically most reactive but at the 8- or 10-positions either of which should be available for the "perhydroxylation" reaction such as occurs with anthracene.

The Intermediate Stages of Benzpyrene Metabolism

It can be easily demonstrated visually that the metabolism of benzpyrene occurs by several steps (Peacock, 1936, 1940; Domach, Mottram & Weigert, 1943; Weigert, 1943). After intravenous injection of benzpyrene into mice the digestive tracts appear fluorescent in ultra-violet radiation. The fluorescence starts at the duodenum, where the brilliantly blue fluorescent bile enters and moves down with the contents along the small intestine. The blue fluorescence of the bile which is different from that of benzpyrene itself, was the first indication that the hydrocarbon is metabolized during its elimination from the body. Peacock (1936) called the blue fluorescent constituent of the bile "BPX". When the contents reach the ileocaecal valve, the fluorescence changes abruptly to green-blue, with spectral bands which are different from those of "BPX". It is this green-blue fluorescent constituent of the faeces which was identified as 8-hydroxy-3 4-benzpyrene, and "BPX", which is an earlier stage of the metabolism, has only a transitory existence in the living animal.

The "BPX" fluorescence appears in the liver and bile and at a number of sites after the application of benzpyrene. The most important of these other sites are the kidney, where the "BPX" fluorescence is confined to the cortex, the lung skin and subcutaneous tissue, after painting or injection of the hydrocarbon. Whereas the typical blue fluorescence increases and disappears again from the inner organs within a few hours it develops much more slowly in the skin and in the subcutaneous tissue, and persists sometimes for days and weeks.

From extracts of the various blue-fluorescent tissues of benzpyrene-treated animals four different metabolites have been separated (Weigert & Mottram, 1943, 1946). Two of them are constituents of "BPX", and were accordingly termed X_1 and X_2 . Two other derivatives, separated from extracts of the large intestine and faeces, were termed F_1 and F_2 . Three main facts which indicate the chemical nature of these derivatives are (a) the absorption spectra of F_1 and F_2 are of the same type as that of benzpyrene itself, whereas the absorption spectra of X_1 and X_2 are of a different type but similar to each other, (b) X_1 appears *in vivo* as the first product of the metabolism if the conversion takes place relatively quickly whereas the production of X_2 proceeds much more slowly, (c) X_1 can be quickly and smoothly transformed *in vitro* with cold alcoholic acid into F_1 . From (a) it follows according to general spectroscopical rules that the five-ring aromatic skeleton of benz-

pyrene is intact in the F-metabolites but not in the X-derivatives, from (c) that in a mild, purely chemical reaction the benzpyrene skeleton, which according to (b) was disrupted during the first step of the metabolism, can be restored. Furthermore, the slow and prolonged production of X_1 indicates that it is preceded by that of X_2 . The metabolism of anthracene is an example of a biochemical disruption and a chemical restoration of the aromatic skeleton, and by analogy it seems probable that a similar biochemical formation of a di-alcohol may occur with benzpyrene.

The absorption spectrum of F_1 is identical with that of 8-hydroxybenzpyrene (Berenblum *et al.*, 1943). That of F_1 is almost the same but for the displacement of the ultra-violet absorption bands by 7 $m\mu$ toward the ultra-violet. As F_1 appears to be a precursor of F_2 , it is very likely that F_1 is a derivative of 8-benzpyrenol (XIII). X_1 may therefore correspond to one of the 1,2-dihydroxy-1,2-dihydroanthracenes, and since it is easily transformed in the cold into F_1 , the constitution of an 8,9-dihydroxy-8,9-dihydro-3,4-benzpyrene with a substituent in the 8-position may be attributed to it (XI). X_2 is slowly produced *in vivo* from X_1 . It appears mainly in the wall of the small intestine and is strongly adsorbed by the cells of various tissues. It is not transformed into F_1 -derivative by mild treatment as is X_1 , but it yields F_1 *in vivo* without passing through the F_1 stage. These properties indicate that in X_2 the 9-hydroxy-group is linked with another group R_1 , as in formula XII. The scheme (formulae X-XIV) shows the probable chemical changes in the metabolism of benzpyrene in mice. Nothing is known as yet about the chemical nature of the groups R_1 and R_2 .

Quantitative Experiments

The problems of the kinetics of benzpyrene metabolism have been attacked by (a) estimation of the rate of disappearance of a known amount of applied benzpyrene from the whole animal or from selected sites (Berenblum & Schoental, 1942; Weil-Malherbe, 1944), and (b) the estimation of the various metabolites at intervals after the application of the hydrocarbon (Weigert & Mottram, 1946). Benzpyrene disappears from the whole mouse after intraperitoneal or subcutaneous injection according to a monomolecular reaction, i.e. the actual amount of the hydrocarbon still present at any moment controls the rate of disappearance. The "half-life" period is about 2 days after intraperitoneal injection in sesame oil, but much longer after subcutaneous injection. The saturation of the blood seems to be the limiting factor controlling the elimination of the hydrocarbon, as the F-metabolites appear at a constant rate during the first 5 days. The excreta contain mainly 8-benzpyrenol (F_1), with a small amount of F_2 during the first day. The discrepancy between the marked slowing of the rate of disappearance of the hydrocarbon (monomolecular rate) and the constant rate of the excretion of the metabolite (zero order), indicates that a mechanism for destruction of benzpyrene in the body exists which is as yet unknown.

After an intravenous injection of colloiddally dispersed benzpyrene into a mouse, about 60% was immediately stored in the liver and the remainder in the kidneys, lung and fatty tissues, and then slowly metabolized and excreted. After the skin of mice was painted with a benzpyrene solution the hydrocarbon disappeared almost completely from the painted area within one day, if the animals were left under normal conditions, but this is due to the material being removed by

licking. If mice were held so that they were unable to lick the benzpyrene, then it disappeared from the painted area very slowly. In both cases X_1 appeared slowly on the painted area and, after reaching a maximum, faded away. This shows clearly that the production of the X-metabolite is due to a local action in the treated tissue. The same process occurs in the kidney and lung and even in the blood. Although the greater part of the benzpyrene metabolites pass out through the small intestine, they do not appear to be absorbed into the blood, but may be fixed in the tissues of the gut as X_1 . If mice are killed immediately after intravenous injection of benzpyrene and bled, the amount of X-metabolites continues to increase in the liver, kidney, lung and in the shed blood. The metabolism of benzpyrene also proceeds in the skin after death. The detached skins from mice were painted with benzpyrene and incubated in Ringer solution at 37°C for one day, when X_1 appeared in the solution (Weigert, Calcutt & Powell, 1946). The yield of X_1 was almost independent of the amount of benzpyrene painted on the same area of the skin, and could reach as much as 20% of the hydrocarbon applied.

After subcutaneous injection of benzpyrene in sesame oil, the hydrocarbon disappeared relatively quickly and some X_1 appeared at the site of injection, but much more X_2 appeared when the hydrocarbon was dissolved in a fraction of mouse fat which, according to Dickens & Weil-Malherbe (1942), inhibits the production of subcutaneous tumours. This means a decrease in the tumour incidence with slow elimination of carcinogen and increase in the formation of X_2 . The X_2 remains in the tissue for many weeks. Similarly, treatment with croton oil, which sensitizes the skin to carcinogens (Mottram, 1944), increases the rate of elimination of benzpyrene and reduces the amount of X_1 fixed in the tissue.

These experiments are consistent with the suggested scheme of the metabolism of benzpyrene, and indicate that the direct quick route from the hydrocarbon via X_1 and F_1 to the end-product of the metabolism is favourable for carcinogenesis, whereas the fixation of the benzpyrene as X_2 in the tissue acts as a kind of detoxication. In any case, these experiments suggest that it is not the hydrocarbon itself which is the proximate carcinogenic agent, but one of the metabolites, either X_1 or F_1 , or the energy released during the transformation from X_1 to F_1 .

Metabolism of Nitrogenous Carcinogens]

When rats are injected with the carcinogenic 2-acetylaminofluorene they excrete 2-acetyl-amino-7-hydroxyfluorene, which was isolated and characterized (XV), in the urine (Bielschowsky, 1945). The metabolism of the carcinogenic azo-compounds probably occurs through the hydrazo-derivatives, as shown to be the case with azobenzene itself (Elson & Warren, 1944). Stevenson, Dobriner & Rhoads (1942) isolated *p*-aminophenol, *p*-phenylenediamine, *p*-acetylaminophenol and diacetyl-*p*-phenylenediamine from the urine of rats dosed with dimethylaminoazobenzene ("Butter Yellow"). One of these metabolic products, *p*-phenylenediamine, and a hypothetical intermediary metabolite, *N,N*-dimethyl-*p*-phenylenediamine, inhibited the enzyme triose-phosphate-dehydrogenase, which is an essential enzyme in carbohydrate metabolism. *N,N*-dimethyl-*p*-phenylenediamine, however, was later shown to be non-carcinogenic (Sugura, Halter, Kensler & Rhoads, 1945), so that it is

improbable that the carcinogenic action of the parent azo-compounds is due to the enzymic inhibitory action of the metabolism products

The metabolism of β -naphthylamine is of interest from the point of view of the hypothesis put forward by the present authors, as this compound appears to induce cancer of the bladder in dogs (Bonser, 1943) and in men, but not readily in other species. Now Wiley (1938) has shown that dogs convert β -naphthylamine to the sulphate of 2-amino-1-naphthol (XVI). On the other hand, Dobriner, Hofmann & Rhoads (1941) were able to isolate 2-acetyl-amino-6-hydroxy-naphthalene (XVII) from the urine of rats, rabbits and monkeys. The metabolism therefore appears to be different in dogs, which are susceptible to this carcinogen, from that in species which are not liable to bladder cancer when treated with β -naphthylamine.

Discussion

The usual metabolism of hydrocarbons in animals involves a hydroxylation process in which a phenol is produced. The phenolic hydroxyl group is usually introduced into the

α -position of the naphthalene nucleus, or into analogous positions in more complex hydrocarbons, in most of which naphthalene can be considered as a constituent part of the larger molecule. It is possible that these phenols are produced through the stages of "perhydroxylation" to a dihydroxy-dihydro-compound or diol, and subsequent dehydration to the phenol. In all the known cases, the hydroxy groups are introduced into positions of the molecule where two adjacent unsubstituted carbon atoms occur, so that the process of formation of the diol and subsequent dehydration to the phenol are possible. The spectroscopical evidence obtained on the metabolism of benzpyrene indicates that such a mechanism occurs in this case, but such diols have been isolated only in the case of anthracene and naphthalene. It is, however, probable that the reaction occurring with anthracene is a general reaction with aromatic hydrocarbons.

There are many known examples of species differences in chemical reactions. The work which has been presented in this review indicates that there are differences in the metabolism of hydrocarbons in different species and under different conditions, and that these differences may be the causes of the differences in response to carcinogenic agents.

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CARCINOGENIC SUBSTANCES IN HUMAN TISSUES

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According to one chemical theory of cancer, some tissue of the body produces a carcinogenic agent by an aberration of those processes which synthesize the steroids, e.g. the steroid group of hormones, and cholesterol and its related compounds. Such an explanation seemed simpler 15 years ago than it does to-day, partly because, since that time, the number of known carcinogenic compounds has increased from 2 to about 300.

But if the relation of the hypothetical endogenic carcinogen to the steroids has become somewhat less obvious, on the other hand, the existence of such a large number of laboratory carcinogens suggests that the investigator has a wider field of possibilities in the search for carcinogenic substances in human or animal tissues.

The problem is being attacked from two directions, namely, the study of the carcinogenicity of steroid hormones,¹ and secondly, the investigation of the nature of carcinogenic substances extracted from the tissues of subjects dead of cancer. Failure to isolate such compounds would not be fatal to the chemical theory, since the view could then be advanced that the carcinogenic agent represents only a transitory stage in a chain reaction, that it might be present at any one time in amount too small to be detected by any means other than its tumour-making power, and that, having stimulated normal cells to neoplasia, it may be rapidly converted to a non-carcinogenic excretion-product. But of course it would be preferable to have positive proof of the agent by demonstrating its presence in the tissues of cancerous subjects and its absence in non-cancerous subjects.²

Some of the problems presented by the carcinogenic substances which have been extracted from human tissues will be solved only when these compounds have been chemically identified and assayed. At the present time, very difficult questions have been raised by the fact that the substances have been found in the tissues from some subjects dead of cancer but not in others, and further, in the tissues of some subjects dead of diseases other than cancer and again not in others.

The admirable work of Steiner (1942, 1943, Steiner, Steele & Koch, 1943) shows that about 20% of the livers of human subjects (death due to cancer or some other cause) contain carcinogenic substances. This result disposes of any simple or direct relation between the presence of the substances and the incidence of cancer in the subject. Of particular value is Steiner's examination of each tissue extract separately, using a separate batch of experimental animals.

Thirty-seven livers from cancerous patients yielded 8 (22%) active extracts, while 6 out of 30 (20%) from non-cancerous patients gave active extracts. This is to say that in a sample of 67 human livers, one in five contains detectable carcinogens.

It would not be very satisfactory to "explain" on a fortunate chance encounter of "1 in 5" why Shabad (Kleinenberg, Neufach & Shabad, 1940, 1941), who was the first to open this line of investigation, found a benzol extract of a non-cancer liver to be inactive while the benzene extract of a cancer liver was active, nor to explain why Sannie, Truhaut & Guérin (1941) found the combined unsaponifiable fraction of 2 cancer livers to be active but the unsaponifiable fraction of 2 non-cancer livers inactive, but it might explain results obtained in this laboratory (Hieger, 1940), where the unsaponifiable fraction of some livers of cancer subjects was highly active³, while similar preparations from other cancer livers were inactive. The essential features of the experiments of these workers and of Menke (1942) have been collected in Tables I-V.

Extracts of the livers of cancerous and of non-cancerous Bantu natives have been found to be carcinogenic by Des Ligneris (1940) in Johannesburg. He obtained 25 tumours, 7 of them malignant, in some hundreds of mice, by painting the skin with a solution of the unsaponifiable fraction of the livers. The unsaponifiable fraction of livers of cancerous or non-cancerous Europeans did not produce skin tumours in mice.

Menke's results in his third experiment are difficult to explain except on the assumption that the extractable fat from the breast diluted the extract from the tumour, or that the still normal part of the breast contained factors inhibitory to carcinogenic action. Alternatively, recourse must be made to the random-distribution observations of Steiner.

Remote Tumours

A number of workers have given attention to the tumours arising at sites other than at the place of injection, here again, Steiner's results, in opposition to those of Kleinenberg *et al* (1940, 1941) and of Sannie *et al* (1941), show little difference in tumour production between preparations from the livers of cancerous and those from non-cancerous subjects, and also surprisingly little difference between preparations which were active in producing local sarcoma and those which were inactive.

TABLE I INDUCTION OF TUMOURS IN MICE BY INJECTION OF TISSUE-EXTRACTS (Kleinenberg, Neufach & Shabad, 1940, 1941)

	Number of mice		Tumours at	
	Initial	Survived after 8 months	Injection site	Other sites
Benzol extract of 41 cancer livers ¹	179	108	4	62
Benzol extract of 26 non cancer livers ²	91	54	0	13
Control	634	389	0	43
Unsaponifiable fraction of 9 cancer livers { x ³	27	13	1	5
{ Rv	23	16	0	25
Benzol extract of lung (unsaponifiable 7) from 19 cancer cases { x	67	46	1	3
{ Rv	28	15	0	6
Benzol extract of lung from 20 non-cancer cases { x	44	26	0	4
	73	32	0	

¹ The cause of death was cancer. (The liver was not necessarily involved)

² The cause of death was not cancer

³ x and Rv represent two different strains of mice

⁴ In one experiment out of 11 mice which survived 11 months, 8 developed sarcomas at the site of injection

¹ [See article in this number by Burrows & Horning (BMB 971) —Ed.]
² The reader is referred to the author's article in *Cancer Research*, 1946, 6, 657 for a somewhat fuller treatment.

TABLE II INDUCTION OF TUMOURS IN MICE BY INJECTION OF TISSUE-EXTRACTS
(Steiner, 1942, 1943, Steiner, Steele & Koch, 1943)

Exp. No.		Number of cases of sarcoma at injection-site	Number of mice injected	Numerator = tumours of lung lymphatic tissue, mamma, uterus, ovary or liver in survivors Denominator = survivors at 6 months
1	Unsaponifiable fraction of 8 cancer livers pooled	12	56	14/30
2	Unsaponifiable fraction of 7 non-cancer livers pooled	5	63	17/54
3	Unsaponifiable fraction of 37 cancer livers, tested separately (8 were found active)	12	456	274 (survivors at 12 months)
4	Unsaponifiable fraction of 30 non-cancer livers, tested separately (6 were found active)	10	440	277 (survivors at 12 months)
5	Benzene extract of a cancer liver	0	32	16/26
6	Benzene extract of 11 cancer livers	0	15	10/14
	A ether soluble fraction	0	67	41/66
	B ether insoluble fraction	0	17	12/17
7	Unsaponifiable fraction of 4 human cancers	0	45	32/42
8	Unsaponifiable fraction of 10 human cancers, large part of cholesterol removed by crystallization	0	35	7/35
9	Sesame-oil control	0	18	—
				Survivors after 12 months
10	Heated sesame oil (350°)	3	31	9
11	Fat from overfried meat	0	20	19
12	Unsaponifiable fraction from overfried meat	0	10	8
13	Benzene extract of overfried meat (excess fat removed by acetone-extraction residue extracted with benzene)	1	20	18
14	Unsaponifiable fraction from above	0	8	7
15	Unsaponifiable fraction of cancer livers and non-cancer livers into rats			

No tumours

TABLE III INDUCTION OF TUMOURS IN MICE BY INJECTION OF TISSUE-EXTRACTS
(Sannlé, Truhaut & Guérin, 1941)

	Number of mice		Tumours at		
	Initial	Survived after 12 months	Injection-site	Other sites	
Unsaponifiable fraction of 2 cancer livers	25	20	6	12	6
Unsaponifiable fraction of 2 non-cancer livers	25	20	0	5	3
Olive-oil control	25	15	0	0	1

TABLE IV INDUCTION OF TUMOURS IN MICE BY INJECTION OF TISSUE EXTRACTS (Hieger, 1940)

Exp. No.		Number of mice		Sarcomas (at injection-site)
		Initial	Survived after 12 months	
1	Unsaponifiable fraction of 3 cancer livers	28	17	11
2	Unsaponifiable fraction of Bantu ¹ livers	30	19	5
3	Ether extract of 2 cancer livers	37 (baby mice)	14	2
4	Ether extract of 2 cancer livers	17 (adult mice)	7	0
5	Benzene extract of 4 cancer livers	60	15	0
6	Unsaponifiable fraction of 3 cancer livers	27	18	0
7	Unsaponifiable fraction of 3 non cancer livers	40	19	0
8	lard (i.e. solvent) controls	303	142	0

¹ For this material which was sent by air I am indebted to Dr. Des Ligniers of the South African Institute for Medical Research.**TABLE V INDUCTION OF TUMOURS IN MICE BY INJECTION OF TISSUE-EXTRACTS** (Menke, 1942)

Exp. No.		a Soxhlet extraction 4 solvents	b Unsaponifiable fraction of a	c Diglucoside fraction	d Flun dig fraction	e Non-carbonyl fraction
		(Numerator = number of sarcomas produced denominator = number of mice)				
1	Breast cancer tumour alone 3 extracts from 3 tumours	7/36	—	—	—	—
2	Cancerous breast after removal of tumour 2 extracts from 2 breasts	0/33	0/18	0/6 ¹	0/6 ¹	—
3	Breast cancer whole i.e. breast + tumour 2 cases	0/18	0/22	—	—	0/18 ¹
4	Non-cancer breast 4 cases	0/54	0/36	—	—	—
5	Rectal cancer	0/15	0/6	—	—	—
6	Osteogenic sarcoma (femur)	1/12	—	—	—	—

¹ Made from the extra. of a separate breast, not the one used for a and b

Effect of Saponification

Kleinenberg *et al* (1940, 1941, Table I) and also Menke (1942, Table V) both found that a simple extraction of tissue with fat-solvents gives an active preparation, while saponification which removes, at any rate in the case of liver, 9/10ths of the total extractable "fat" fails to give a product of increased potency. Thus no hint is given whether the agent belongs to the fatty glycerides and phospholipins or to the steroids. Steiner (Table II), on the other hand found that, in one series of experiments, 15 livers pooled in two groups of 7 and 8 gave strongly carcinogenic unsaponifiable fractions, but that the benzene extracts of 11 pooled cancer livers were inactive. It would be very curious if the first two groups (7 and 8 livers) happened to contain one or more of the active livers which occur once in 5 times, while the third group of 11 livers did not contain a single one of these active livers. Alternative explanations would be that saponification concentrated the agent by removing inactive fats, or that the active agent was an artifact.

Steiner's preparations were obtained by somewhat drastic means, namely saponification at the boiling point with potash for 18 hours. Such treatment might conceivably form a carcinogen from a precursor or might destroy a carcinogen already present but since all of his 67 livers were treated in the same way, the evidence is in favour of a very stable carcinogen, present infrequently (namely, 1 in 5). It may be possible in the future to apply less drastic methods to the analysis of tissue fats, such as chromatography or the centrifugal molecular still.

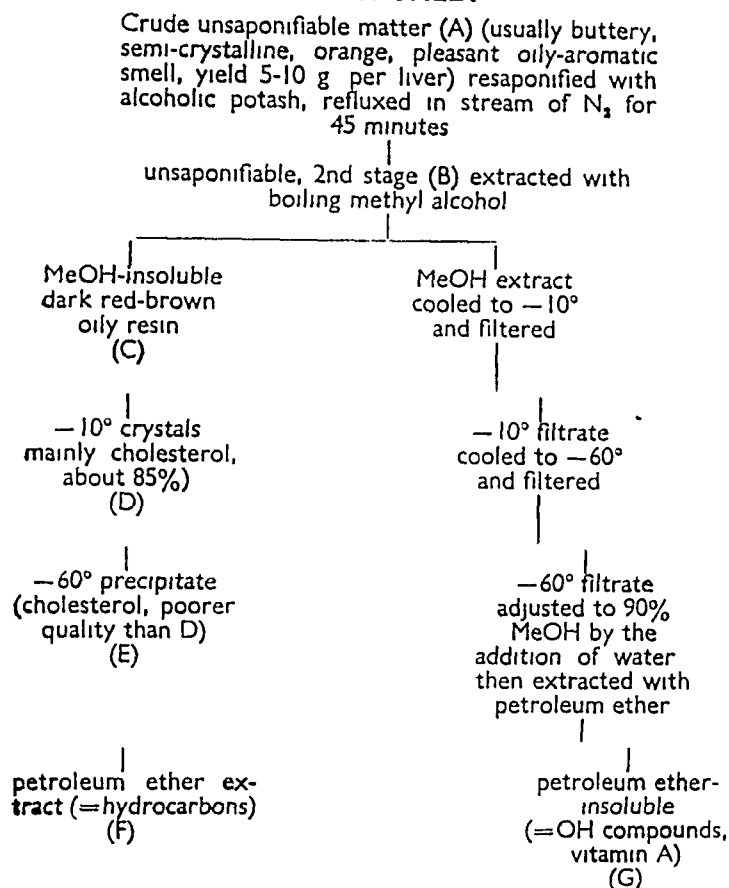
In experiments carried out here 2 sarcomas were produced in 37 mice injected from the second day after birth with an ether extract of cancer liver. (The same extract injected into 17 mice 7 weeks old produced no tumours.) Menke (1942) and Steiner carried out the obvious test of using the same preparation for making (a) the simple extract and (b) the unsaponifiable fraction. In Menke's experiments and in one of Steiner's neither (a) nor (b) were active, but in Steiner's overfried meat experiment (No 14) (Table II) the unsaponifiable fraction was inactive but the simple benzene extract produced one sarcoma. Thus, while Steiner (Table II) and Hueger (Table IV) show that saponification nearly always gives products of higher potency than does simple extraction one critical test (based on a single positive result)

suggests the reverse Menke tries to compromise by proposing that there are two agents, one in the saponifiable part and one in the unsaponifiable

Fractionation of Unsaponifiable Material from Tissues

The chemistry of the carcinogenic factor was investigated in our Institute by fractionating the unsaponifiable matter from human liver by a much simplified form of the technique used in preparing vitamin-A concentrates from liver. The steps are indicated in the flow-sheet

FLOW-SHEET



Soon after this work had been begun, Kleinenberg, Neufach & Shabad (1941) reported the production of a tumour in a mouse with an extract, not of liver, but of the lung of a subject dead of cancer. In the experiments carried out here it was decided that, in order to obtain enough material for preparing the unsaponifiable fraction, a mixture of the larger organs and tissues other than liver might be used. Lungs, kidneys and skeletal muscle were removed post mortem and treated together in the same way as liver.

Little attention was given to the particular type of cancer involved. The immediate aim was to find the physico-chemical nature of the active substance, although the possibility remained that different tissues might contain different carcinogens. Non-cancer tissues were from elderly or middle-aged subjects dead of any cause other than cancer.

The livers or other tissues were placed in the cold room as soon as possible after removal from the body. They were usually saponified on the next day, but sometimes 2 or 3 days elapsed between death and the processing of the tissues, by which time they were usually frozen solid. The survival rate of the active substance in dead tissue is unknown, but a compound which will withstand boiling alcoholic caustic

potash for 3 hours is not very likely to be decomposed by tissue enzymes near freezing point.

Controls

1. In control experiments, in which some hundreds of mice were injected with the solvent (lard) alone, no tumours have been obtained (Table IV). These control mice were treated otherwise by exactly the same technique as those in which the tissue fractions were tested.

2. Tests are in progress to see whether carcinogens are produced as artifacts during saponification, since two workers (Steiner and Hieger) found that activity was increased by this process, or, more exactly, the unsaponifiable fraction of livers has proved much more carcinogenic than crude fatty extracts. Alcohol, and especially industrial spirit, contain traces of acetaldehyde, which is resinified by alkali, and this resin, being soluble in ether, would be found in the unsaponifiable fraction. In three experiments, distilled spirit, distilled alcohol, and alcohol to which acetaldehyde had been purposely added, were refluxed with potash for 3 hours in quantities adjusted to imitate the conditions of liver saponification. The testing of these resin-products in mice has now been in progress for 20 months.

3. Cholesterol undergoes oxidation in alkaline solution. 10 g of cholesterol (i.e. about twice as much as is contained in a human liver) were refluxed with potash and (a) alcohol, (b) spirit, in a control experiment, no liver tissue being present. The testing of the products in mice has now been in progress for 14 months.

4. The active fraction (D, see flow-sheet) consists largely of cholesterol. Commercial cholesterol, suspended in lard in 25% concentration, was therefore injected into mice. 132 of 5 different strains of mice have been treated, and although many died early in the experiment, a single C₃ mouse developed a typical spindle-celled sarcoma at the site of injection in 11 months. This tumour has now reached its 16th generation and grows with unusual speed for, if allowed it will reach the size of the mouse in a month.

Technique

No polycyclic hydrocarbons were allowed in the laboratory. As has been pointed out earlier, some aerial contamination by soot or other carcinogenic substances was practically unavoidable owing to the position of the Institute and the laboratory. Where practicable, apparatus and materials were protected from atmospheric dust by the plentiful use of clean paper covers during the experiments. Solvents were distilled over eosin, which could be detected in the distillate by ultra-violet fluorescence if traces were sprayed over. Solid reagents were not to be so easily purified, they were used at analytical-reagent quality and washed with distilled ether when required. Nevertheless, all such precautions were obviously far from perfect.

Injection

As far as possible the fractions were injected dissolved in lard at 15% concentration, except where little of a fraction was available and economy had to be exercised. Injections were made subcutaneously in the flank, either 0.1 cm³ or 0.2 cm³ fortnightly, the object being to maintain a reservoir of material which could be felt through the skin as a soft nodule. In some cases, after 5 or 6 injections no further injection was needed for a year or more, in other cases, the reservoir had to be replenished more frequently.

Sarcoma Production

Unless otherwise stated, the mice used in all the work summarized in Tables IV and VI, and for testing the fractions shown in the flow-sheet, were mixed commercial stock of unknown heredity obtained from the same source (Parallel tests on mice of the C₁₇ strain are in progress and will be reported on later)

TABLE VI SARCOMA PRODUCTION WITH CRYSTALLINE, CHOLESTEROL-RICH FRACTION D (see flow-sheet)

Tissue	Number of mice		Tumours	
	Initial	Survived after 12 months	Number	Latent period (months)
Non cancer (lung-kidney-muscle)	25	14	2	15 24
Cancer (lung kidney muscle)	25	10	3	14 15 20
Cancer (liver)	10	9	2	16 19
Non cancer (liver)	20	8	0	—

The control series receiving lard only have so far given negative results, but some of the tests are still in progress. The results obtained with fraction D of unsaponifiable material obtained from various cases are given in Table VI. The tumours were spindle-celled sarcomas at the site of injection. The negative result with fraction D of non cancer liver is noteworthy and this test will be repeated. With one exception the tumours (i.e. 7 out of 8 in 231 mice) occurred in the series injected with fraction D (see flow-sheet) irrespective of its origin i.e. whether the tissue was liver or lung-kidney-muscle or whether the tissue was from cancerous or non-cancerous subjects. Moreover, the activity of the fraction D obtained from 3 different sources was of the same order but the precise significance of this similarity is unknown for the conditions of the test may be such that large relative differences in agent do not effect proportionate differences in potency. The eighth tumour was produced by fraction B from non-cancer lung-kidney-muscle mixture (see flow-sheet).

Cholesterol estimations on fraction D from different sources by digitonin precipitation, give figures ranging from 74% to 92% cholesterol which are probably rather high, since the digitonin method does not distinguish between cholesterol and other 3(β)-hydroxysteroids. Dr Shoppee (private communication) working with a large sample (30 g) of fraction D finds a cholesterol content of 85% based on the isolation of chromatographically pure cholesterol

acetate m.p. 115°, (n_D^{20}) = $-43.6^\circ \pm 1^\circ$

This fraction (D) will be considered then to have a cholesterol content of about 85%, it contained no saponifiable material and was a somewhat waxy crystalline powder, of the colour of pale straw or orange and obviously not homogeneous, for the coloured part seemed to be unevenly adsorbed on the white part. It remains to be determined whether the active substance is present in small amount adsorbed on to the cholesterol during crystallization, or whether, along with the cholesterol are crystallized appreciable amounts of allied sterols or sterol derivatives among which is the factor whose identity is required. Possibly the cholesterol itself which makes up the larger part of this fraction is by no means inert in sarcoma production, and the tumour may be the end result of the combined activity of more than one compound. Thus the carcinogenic activity of benzpyrene is increased when cholesterol is added according to the results of experiments by Dickens & Weil-Malherbe (1945), in which solutions of the hydrocarbon with and without cholesterol were painted on mice. The chemical constitution of the compounds associated with cholesterol contained in fraction D is being investigated by Dr Shoppee in this Institute, who will publish his results shortly.

Sub-fractions of this fraction are undergoing tests in mice.

Summary

1 Previous work is reviewed and attention is drawn to the main difficulties in this field of investigation

- The low potency of human tissue carcinogens as indicated by a prolonged latent period,
- the sporadic occurrence of these substances (Steiner),
- the uncertainties with regard to 'susceptibility' of the experimental mice

2. A technique of fractionation of unsaponifiable material from tissues is described.

3. A sarcoma-producing fraction has been obtained from mixed lung-kidney-muscle of cancerous and non-cancerous human subjects, and from the liver of cancerous subjects

4. The carcinogenic substances from these 3 sources are found in the cholesterol-rich fraction of the unsaponifiable material. This fraction is a crystalline mixture of compounds containing on the average about 85% cholesterol

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THE CARCINOGENIC ACTION OF HEATED FATS AND LIPOIDS

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There is now sufficient evidence to justify the title of this article, but to present it fairly is no easy task as there has been much speculative writing on the subject. There has been a number of isolated or unsupported reports of tumours, but, on the other hand, evidence of importance is sometimes to be found only in papers devoted mainly to other considerations, as its significance was not apparent at the time of writing. It may be, therefore, that some important data have been overlooked in presenting the evidence, but an attempt will be made to correlate data from various sources and to present the development of this line of research as seen by the writer. Several critical reviews have appeared covering various aspects of this subject, and reference will be made to them.

The fact that carcinogenic properties can be conferred on naturally-occurring organic substances by destructive distillation at high temperatures was first recorded by Kennaway (1924), who prepared carcinogenic tars from yeast and from human skin at temperatures between 700° and 920° C. Kennaway & Sampson (1928) prepared a carcinogenic tar from cholesterol heated under the same conditions. Although of great scientific interest and of possible importance as an industrial risk, such procedures were far removed from metabolic processes. Kennaway (1930) therefore sought to devise less drastic chemical methods of preparing carcinogens at body temperature, but without success, for though he obtained from the reaction of AlCl_3 with tetralin, at 37° C, a mixture of substances with a high boiling-point which yielded carcinogenic distillate at a temperature of 270° C, the undistilled material was not carcinogenic.

Following the discovery by Kennaway and his associates of the carcinogenic potency of pure 1,2,5,6-dibenzanthracene—the first substance of its kind to be recorded—extensive animal tests were carried out by the London Cancer Hospital group (Cook, Hieger, Kennaway & Mayneord, 1932), both by painting on the skin and by subcutaneous injection. As dibenzanthracene, like other hydrocarbons, is insoluble in water, they employed lard or olive oil as convenient vehicles for subcutaneous injection of dibenzanthracene in rats and mice. In order to extend this investigation, Burrows (1933), in the same department, injected two fowls with a similar preparation of dibenzanthracene dissolved in heated lard, and one of these birds developed a spindle-cell sarcoma at the site of injection.

At about the same time, the writer (Peacock, 1933) independently carried out a similar experiment on 30 fowls, but injected dibenzanthracene dissolved in heated lard in the

right pectoral muscles, and heated lard only in the left side. Both portions of lard were simultaneously heated on the same hot plate to 140° C for 30 minutes, during the solution of the dibenzanthracene crystals, and both were cooled to 40° C before injection. Seven birds developed sarcomata on the right side (dibenzanthracene) and 3 on both sides. As each injection was checked by two assistants, and as other precautions were adopted to avoid any possibility of confusion in the injections, this result seemed to indicate either that lard heated to 140° C for 30 minutes was carcinogenic, or that it in some way determined a remote carcinogenic action of dibenzanthracene. To elucidate this unexpected result, the writer initiated research which is still in progress, and has yielded evidence of carcinogenicity in fats and in cholesterol after heating to 270° C or more (Beck, 1941, Beck, Kirby & Peacock, 1945). But no further evidence of carcinogenic action of lard heated at 140° C has been found. Lard is unfortunately not a constant mixture, and qualitative differences between samples probably account for some of the variable results reported by different investigators.

Burrows, Hieger & Kennaway (1936) published the results of extensive experiments with lard, olive oil, and other fatty materials in rats and mice, some of which they had mentioned in an earlier publication (1932) when the results were negative. No tumours were induced in mice by any of the fats and lipoids tested, but 12 out of 217 rats developed spindle-cell tumours at the site of injection, though the authors were cautious in classifying them as malignant tumours. Five of these tumours occurred at the site of control lard injection, and 2 at the site of lard containing 5% oleic acid or theelin respectively. These authors also tested lard previously heated to 340–360° C in a stream of nitrogen, and then extracted with petroleum ether and aqueous sodium carbonate. The petroleum ether was removed by distillation in CO_2 and the alkaline extract was acidified and the precipitate so formed was washed with water, dried, and mixed with lard in the proportions of 1:3. Both these fractions were injected into rats and mice. No mouse tumours were observed, but 1 of the 6 rats surviving one year after injection with the petroleum-ether-soluble fraction developed a large tumour which was autografted and grafted into an unspecified number of animals, but without success. The rat died soon afterwards without metastases, "but the tumour showed spindle-celled areas, but was mostly of a more fibromatous character than are the great majority of tumours produced in connective tissues by carcinogenic hydrocarbons".

The alkali-soluble fraction also yielded one tumour which was more "cellular" but which could not be propagated by grafting. In the foregoing experiments, elaborate precautions were taken against possible contamination of apparatus or animals by traces of chemical carcinogens, the wisdom of such precautions became more evident in the light of subsequent experience. Although the London Cancer Hospital group hesitated to describe these tumours as sarcomata in the absence of metastases or successful grafting experiments, their illustrations show locally-invasive tumours which, judged in the light of later work, merit, in the writer's opinion, a classification of sarcoma.

These results are given in some detail, as they seem to be the first records of neoplastic growth induced by naturally-occurring fats heated within the range of temperatures that can occur in domestic cooking. This aspect was not stressed by the authors.

Thus ten years ago there was a *prima facie* case against heated lard as a potential carcinogen (using this term to cover the induction of all kinds of malignant tumours)¹

About this time the obvious implications of the available facts about carcinogenic hydrocarbons and heated lard led the writer (and no doubt other investigators) to study methods of cooking in heated fats and oils. The high incidence of gastric cancer in human beings as contrasted with the very low incidence in all other species as far as is known, points clearly to some essentially human habit or attribute as of aetiological importance. The variations in incidence of gastric cancer in different human communities, however point rather to habits than to inborn human qualities as being mainly responsible. For example the incidence of gastric cancer is about twice as high in Holland, Sweden and Denmark, as in Britain, while within Britain the incidence varies as greatly in different economic groups, being highest in the poorest classes. (For critical discussion, see Cramer, 1936, Peacock, 1943)

Roffo has written extensively on the subject of heated fats and cholesterol as carcinogens, and claims to have induced cancer of the squamous-lined forestomach or rumen of rats, which has no human counterpart, and in the glandular stomach by feeding them with several heated fats and heated cholesterol. While some of Roffo's results (1938) are in accord with those of other investigators, his evidence in regard to the induction of gastric adenocarcinoma seems to be inadequate. Moreover his spectrographic evidence for the formation of benzpyrene in heated fats and cholesterol has been adversely criticized by Cook & Kennaway (1940) and is contrary to the experience of the writer and his colleagues. (Roffo's work was also criticized in a review by Klem & Palmer, 1941)

Minimal Effective Concentrations of Carcinogens

At this point it is desirable to consider some technical difficulties of investigating minimal effective quantities of carcinogens. Shear (1936) has recorded the induction of a sarcoma in a mouse at the site of implantation of a cholesterol pellet containing 0.4 gamma of 1,2,5,6-dibenzanthracene. This seems to be the smallest recorded effective dose of a known carcinogen, and as judged by gravimetric standards it is indeed small. Yet it represents approximately one thousand million molecules of dibenzanthracene. By spectrographic methods a solution containing one part in ten million of benzpyrene in acetone can be distinguished from the solvent alone, yet for practical purposes one cannot easily work with less than 0.1 ml of such a solution, which would contain about 0.01 gamma, or roughly 20 million molecules, of benzpyrene. Below this level it is not possible to detect the presence of benzpyrene with certainty by current methods of analysis and even if our methods should become a million times more sensitive it would still be impossible to identify quantities of a million molecules of benzpyrene in an extract. As the theoretical limit for carcinogenesis would be the action of one molecule of carcinogen on one cell it must be recognized that failure to identify any known carcinogen, in a substance that has been shown by animal tests to be carcinogenic does not exclude the possibility that this action may be due to the presence of some millions of molecules of a carcinogenic hydrocarbon.

¹ This is justifiable etymologically as *karkinos* was the Greek word for crab (Latin *cancer*) at a time when histological classification was impossible.

It is urgently necessary therefore, to investigate the lowest effective dilution of pure chemical carcinogen and until this has been carried further we cannot afford to be dogmatic about the nature of the carcinogenic action of heated fats.

In judging the results of injection of heated fats and lipoids, the foregoing facts must be borne in mind, and it must be realized that to talk of "weak carcinogens" by comparison with such substances as benzpyrene and methylcholanthrene may give a false impression, as these pure substances in detectable amounts must rarely constitute a risk outside laboratories and certain industrial plants.

Table I summarizes the results of tests conducted in this laboratory. It will be noted that there is no positive evidence of carcinogenic properties in fats or cholesterol heated at less than 270° to 300° C. This is in keeping with Kennaway's early observations on the carcinogenicity of various fractions of synthetic tars. He set the limit of 270° C, "which temperature appeared to indicate very roughly the boundary between the lower-boiling, non-carcinogenic and higher-boiling fractions." In the same paper (1930) he describes carcinogenic fractions of synthetic tars prepared from tetralin after distillation between 205°-260° C, but not with lower-boiling fractions.

A number of other investigators have reported similar results to those obtained here. Reference to these may be found in the comprehensive reviews of Cook & Kennaway (1938, 1940) and of Cook, Haslewood, Hewett, Hieger, Kennaway & Mayneord (1937).

Feeding-experiments have given less satisfactory results. We described (Beck & Peacock, 1941) a condition of gastropapillomatosis in rats fed on an apparently adequate diet to which heated lard had been added. The fat was either heated at 220° C for 12 hours or at 350° C for $\frac{1}{2}$ hour under conditions similar to those in domestic cooking. This result was complicated by the fact that the diet induced avitaminosis-A by interfering with the storage of the vitamin in the liver. As similar lesions of the stomach can be caused by a wide variety of dietary deficiencies this type of result cannot be regarded as satisfactory evidence of carcinogenicity. Large-scale tests of heated lard were carried out by Morris, Larsen & Lippincott (1943) who failed to obtain gastric tumours in rats receiving as much as 50% of lard heated at 300° C for 2 hours or at 350° C for $\frac{1}{2}$ hour, though they induced chronic gastric ulcers and fatty degeneration and cirrhosis of the liver.

The failure of such experiments does not preclude the possibility that heated fats may have some relation to the aetiology of gastric cancer, and it seems possible in the light of present-day knowledge that the presence of even undetectable amounts of carcinogens in the diet over a long period of years might induce tumours under the influence of other substances as co-carcinogens. The way in which croton oil or resin can develop the action of sub-effective amounts of carcinogenic hydrocarbons was well illustrated by Mottram (1944), shortly before his death. Although croton oil is rarely used therapeutically and is never an article of diet there may well be other, unsuspected, co-carcinogens in common use which could develop the action of sub-effective doses of carcinogens.

Light on possible modes of action of fat-soluble carcinogens comes from experiments of yet another kind. The natural route for elimination of many fat-soluble water-insoluble

TABLE I

Author	Substance	Temperature and time of heating	Method of Administration	Yield of tumours	Nature of Tumour
Beck (1941)	Cottonseed oil	340°-360° C 1 hour	0.5 ml subcutaneously	(12) 2/6	spindle-cell sarcomas after 414 and 538 days
	Cottonseed oil	200°-220° C 12 hours	0.5 ml subcutaneously	(12) 0/3	—
	Cottonseed oil	Unheated	0.5 ml subcutaneously	(12) 0/10	—
Beck, Kirby & Peacock (1945)	20% cholesterol in olive oil or cottonseed oil	270°-300° C ½ hour	0.5 ml subcutaneously	(18) 1/8	spindle-cell sarcoma after 386 days
	20% cholesterol in cottonseed oil	270°-300° C ½ hour	painted	(12) 0/12	—
	Residue from heated cholesterol 20% in olive oil	270°-300° C ½ hour	0.5 ml subcutaneously	(12) 1/11	spindle cell sarcoma after 345 days
	20% cholesterol stearate in arachis oil	300° C ½ hour	0.5 ml subcutaneously	(18) 0/18	—
	25% cholesterol palmitate in arachis oil	300° C ½ hour	0.5 ml subcutaneously	(24) 0/24	—
	20% cholesterol in arachis oil	430° C ½ hour	0.5 ml subcutaneously	(18) 0/18	—
	17% cholesterol in acetone	430° C 1 hour	painted	(18) 3/4	2 regressing 1 persistent papilloma earliest 460 days

NOTE—The numbers in brackets give the initial numbers of mice under test. Fractions give the ratio of tumours to animals surviving at the time of the first tumour's appearance.

substances, including carcinogenic and non-carcinogenic hydrocarbons, is mainly by way of the liver, biliary passages and alimentary canal (Peacock, 1936). Chemically stable fat-soluble substances ingested over a long period would probably reach a higher concentration in the liver than in most other tissues. Shabad (Kleinenberg, Neufach & Shabad, 1940) first drew attention to human liver as a source of carcinogens, and his work has been confirmed by independent investigations (Hieger, 1940, Des Ligneris, 1940, Steiner, 1942), though the nature of these substances has not yet been determined. The carcinogenic material is present in the unsaponifiable and fat-soluble fraction of the liver, but it has not yet been established whether there is regularly a higher concentration of potential carcinogen in the liver of cancer patients than in the liver of non-cancer patients of similar age-groups, though the available evidence suggests that this may be so. It is quite possible that this apparently endogenous source of chemical carcinogens is really of exogenous origin and is merely accumulated in the liver. At any rate it does not seem to come from the tumour, as tumour-extracts prepared in the same manner are non-carcinogenic.

Steiner (1942) makes the interesting point that, if cancer is viewed as a disease of individual cells, then the risk to individual epithelial cells of the human extra-hepatic biliary passages is much greater than that to gastric epithelial cells, as the total cell populations of the two organs are roughly in

the proportion of 1:300, whereas the incidence of cancer is about 1:60. This seems to suggest that the bile would be a better source of potential carcinogens than liver, but so far there is insufficient evidence to determine this point. Small-scale investigations of samples of bile from cancer and non-cancer groups of patients in this laboratory have not given any evidence of the presence of carcinogens in either group of samples. In this connection it should be remembered that, in the case of benzpyrene, excretion of the hydrocarbon by the liver is effected by metabolism to 8-hydroxy benzpyrene, though about 1% is excreted unchanged (Peacock, 1936, Chalmers & Peacock, 1936, Chalmers & Kirby, 1940, Chalmers & Crowfoot, 1941).

Evidently we are only beginning to understand how carcinogens may be derived from seemingly harmless articles of diet, and even from apparently normal tissues, and it is by no means certain that any of the common forms of human cancer are, in fact, caused by such potential carcinogens. However, it is the purpose of cancer investigators to reduce the risks of carcinogenesis, and to this end any substance that has been proved to be carcinogenic, or any tissue of any species of animal, must be regarded as potentially carcinogenic for other tissues and other animals. Judged on this basis, which may err on the side of safety, methods of cooking that involve heating fats and oils to temperatures about 300° C provide a source of potential carcinogens.

Continued at foot of page 357

OESTROGENS AND NEOPLASIA*

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- 2 Pituitary tumours
- 3 Mammary cancer
- 4 Uterine fibromyomata
- 5 Uterine adenomata and carcinomata
- 6 Ovarian tumours
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An oestrogen is any chemical compound which will induce cornification of the vagina in an adult mouse, like that which occurs at normal oestrus. Such compounds are formed naturally in the ovaries, placenta, adrenals and testes. In addition, numerous oestrogens, which are unknown as natural products have been synthesized. These compounds, natural or artificial, all act alike in the body, though the

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CARCINOGENIC ACTION OF HEATED FATS AND LIPOIDS

Continued from page 366

Tests in the kitchen of the Glasgow Royal Cancer Hospital showed that the temperature of fat used for deep frying did not exceed 250° C, but frying in an open pan, and roasting and grilling may expose the surfaces of fatty foods to higher temperatures. It is not unreasonable, therefore, to consider whether the statistical evidence in regard to human cancer, particularly

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speed and duration of the results, and the effective quantities of drug, vary with their rate of solution and metabolism, and with the special characters of the recipient. However, every oestrogen has two noteworthy biological properties: (i) it acts specifically on structures concerned with reproduction and (ii) in certain conditions it may be a cause of tumours in these organs. Although the neoplastic influence of oestrogens is not quite limited in this specific way—for they may bring about subcutaneous sarcomata, leucaemias, and tumours of bone—yet the limitation is close enough to form a characteristic feature.

In one respect the carcinogens and gonadal hormones overlap in their potencies, for, according to Bullough (1946) oestrogens, androgens and carcinogens all stimulate mitosis throughout the body. The cells of the female reproductive system, however, are peculiarly sensitive to oestrogens, as those of the male organs are to androgen.

In Fig 1 are structural formulae of some of the best-known natural oestrogens, and for comparison the constitutions of some other natural compounds are shown in Fig 2. For consideration with these several artificial oestrogens are shown in Fig 3.

1 Actions of Oestrogen on Tissue-growth

1 Arrest of Normal Tissue-growth

In some circumstances the growth of particular tissues is prevented by oestrogens. Thus, they check the supply of follicle-ripening hormone from the anterior lobe of the pituitary and so stop the development of the ovarian follicles, or, when present in excess, oestrogens impede rather than enhance the growth of the mammary ducts.

11 Stimulation of Growth of Special Organs

Specificity of action. The stimulating effect of oestrogens as already said is mainly confined to the female organs of reproduction. This specificity is independent of the sex of

of the alimentary canal, can be further correlated with experimental data, and, if so, whether modification of cooking methods designed to prevent or minimize the cooking of food at temperatures above 250° C would not be justifiable. Clinical research based on a thorough investigation of life long dietary habits might yield useful information on this subject.

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FIG 1 SOME WELL-KNOWN NATURAL OESTROGENS

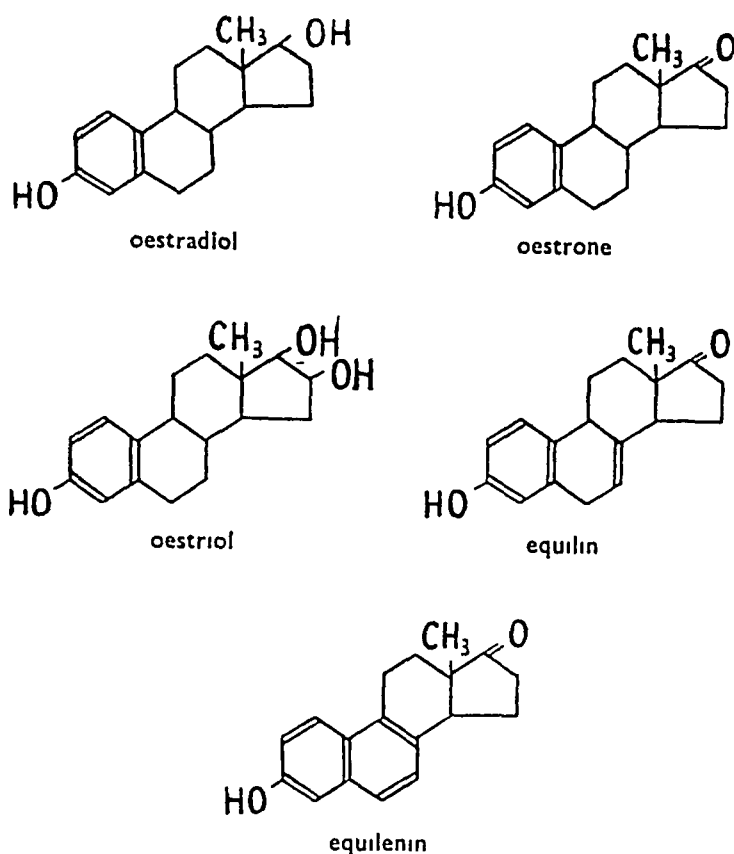


FIG. 2. SOME NATURAL NON-OESTROGENIC STEROIDS TO COMPARE WITH THE OESTROGENS OF FIG 1

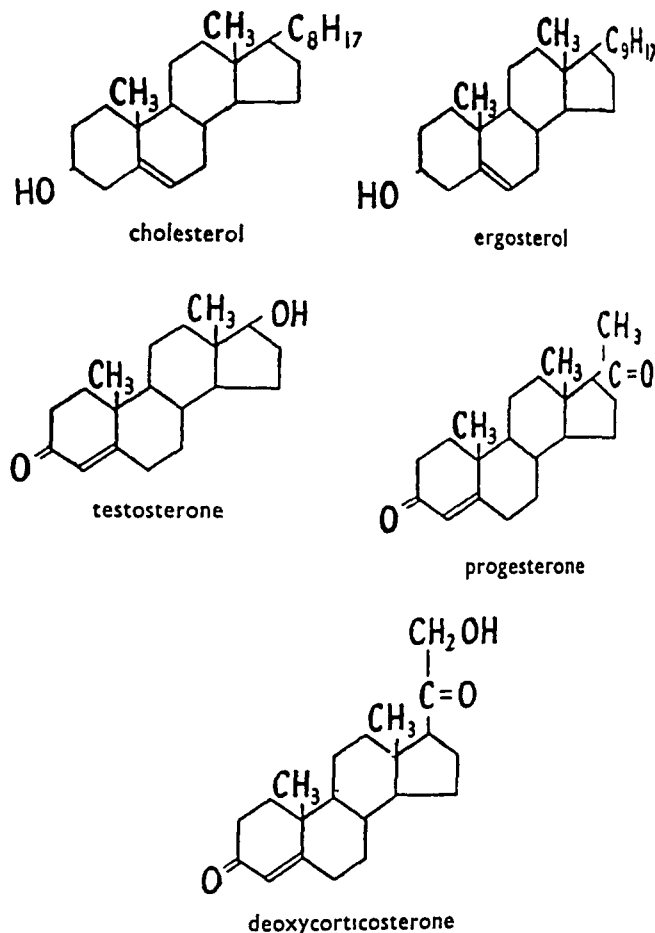
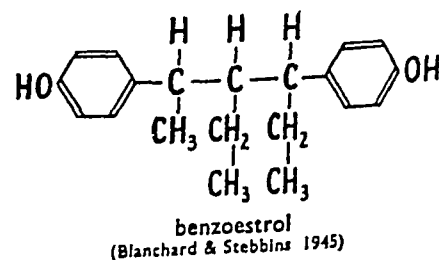
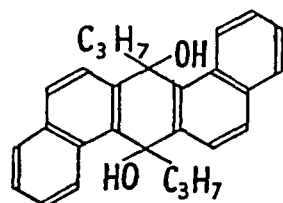
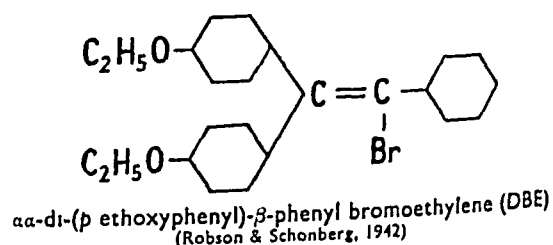
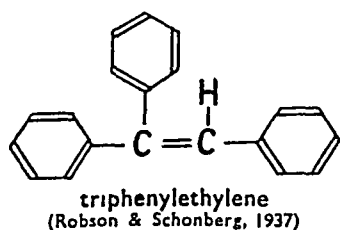
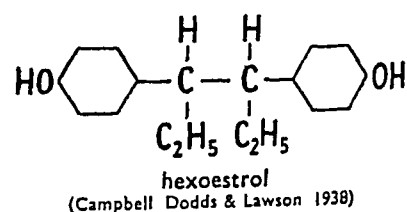
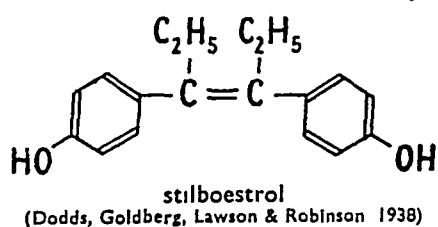


FIG 3 SYNTHETIC OESTROGENS



the individual, and homologous tissues in the two sexes react alike, the capacity to respond is innate in each individual cell, is unaffected by its neighbours, and is not abolished by transplantation into another part of the body or into another individual, whether of the same or the opposite sex.

Gradients of responsiveness The potency of an oestrogen varies in degree, not only as between one organ and another but also in different parts of a single organ.

Localization by hyperaemia and inflammation For obvious reasons hyperaemia will probably enhance the local effectiveness of a hormone carried in the blood-stream, and inflammation certainly causes an increased concentration of oestrogen in the affected region (Brunelli, 1935). Perhaps the observation by Wade & Doisy (1935) that daily swabbing alone may induce oestrogenic effects in the spayed rat's vagina may be explained on this foundation for spaying does not lead to a total disappearance of oestrogen from the blood.

Reversible and irreversible effects After adolescence, though not before, most of the effects of oestrogen are reversible and to such a rule innocent tumours conform, in this respect cancer is exceptional.

Effects of sex and repeated administration. Results obtained by Steinach & Holzkecht (1916), who transplanted the testes of guinea-pigs into females, and ovaries into males, seem to indicate that males are more reactive than females to oestrogens, on the other hand some adaptational resistance to oestrogen in a male mouse after prolonged administration has been recorded (Burrows 1937).

Inactivation and excretion of oestrogen The effects of an oestrogen depend for their degree upon the rate of its inactivation by the liver and its excretion by the kidneys and bowel. These processes have obvious implications. The occasional appearance of gynaecomastia in men with hepatic cirrhosis seems to illustrate the statement. The action of the thyroid and the general metabolic rate also have to be considered.

Other factors concerned with the appearance of oestrogenic effects There is not space here to enumerate every detail affecting the degree and nature of oestrogenic action. The hindrance to the production of oestrogen and the antagonism to some of its effects displayed by androgen is one of these and so, too, might be mentioned the various co-operative and antagonistic effects of the gonadotrophins toward each other. Later we shall have occasion to remark that ill-health, and especially that due to a deficient food-supply, materially reduces the production of oestrogen in the living organism and consequently reduces the liability to oestrogenic cancer.

Bearing in mind this summary of facts, attention may be given to the neoplastic effects of oestrogens.

2. Pituitary Tumours

The cells of the anterior lobe of the pituitary gland respond to oestrogens by a considerable variation in their numerical proportions and cytological characters. Chromophil cells for instance diminish in numbers with a corresponding increase of the chromophobe cells. These changes may, if sufficiently prolonged, give rise to enlargement of the anterior lobe as a whole. Under conditions of excessive stimulation the gland passes ultimately into an exaggerated state of hyperplasia, having the characteristics of an adenoma. In the literature on experimental induction of pituitary tumours and their spontaneous occurrence in certain strains of rats

there is some confusion as to which tumours may be classified as true adenomata and which should really be placed in the category of functional hyperplasias.

Spontaneous tumours of the pituitary gland occur frequently in male and female rats of certain strains (Martins, 1936; Wolfe, 1941; Saxton & Graham, 1944) and rarely in other strains. In mice these tumours are rare, the incidence being so low that for instance according to Slye, Holmes & Wells (1931) only one such tumour was found in 11,000 mice. Wolfe (1941) noted in an inbred strain of rats that advancing age was associated with reduction in the acidophil cells and a progressive enlargement of the gland as a whole. Similarly Saxton & Graham (1944) recorded the appearance of chromophobe adenomata in 61% of males and 30% of females of the Yale strain. There is some doubt whether these authors were dealing with true adenomata. The spontaneous enlargement was inhibited according to Wolfe (1941) by repeated daily injections of testosterone propionate. Saxton & Graham (1944) made homologous intra-ocular transplants and concluded, however, that the tumours could be more closely identified with neoplasia than with focal hyperplasia although they produced no evidence of actual metastasizing new growths. There is no doubt that, in some strains of rats ageing is accompanied by a hormonal imbalance sufficient to cause growth and cellular changes in the pituitary gland the swellings of which in some instances may resemble adenomata.

In 1936 the formation of pituitary tumours in mice and rats after prolonged oestrogen administration was described (Cramer & Horning, McEuen, Selye & Collip, Zondek). These results were confirmed by Burrows (1936a) and Deansley (1939) among many others. Burrows (1936b) treating mice over long periods with oestrone, has obtained nodulated pituitary tumours which occupied one-third of the cranial cavity, and in some cases caused exophthalmos with other obvious physical signs. None of these workers was able to claim, however, that the tumours metastasized or possessed all the characters of true neoplastic growths. Deansley (1939) found that if the oestrogen treatment was stopped, the glands gradually returned to their normal size even though they had been stimulated by the oestrogen to adenomatous dimensions. The condition was therefore maintained only in the presence of excessive amounts of oestrogen and could be reversed or even inhibited at the outset as Cramer & Horning (1938) showed by the simultaneous injection of thyrotrophic hormone with the oestrogen.

It should be noted that the hyperplastic reaction caused by excess oestrogen as far as the present evidence shows is confined to rodents and it cannot be said that oestrogen invariably induces the same type of response. Stilboestrol stimulates the formation of acidophil cells according to Baker & Everett (1944) whereas naturally-occurring oestrogens increase the number of basophils (Declin, 1935; Severinghaus, 1936). By treating different inbred strains of mice with oestrone from birth Lacassagne & Nyka (1937) showed that the pituitary gland in each strain reacted differently to equal doses of the same hormone. These observations were confirmed by Gardner & Strong (1940).

Vazquez-Lopez (1944), working with the hamster, *Cricetus*, has succeeded in inducing an adenoma-like hyperplasia of pars intermedia cells by prolonged oestrogen administration which in its early stages recalls the spontaneous basophil invasion of the pars nervosa found not uncommonly in the

human gland Unlike the anterior lobe tumours, described in rats and mice by previous authors, there is much more invasive growth by the tumours in hamsters The cells extend in some cases into the anterior lobe, throughout the pars nervosa and upwards through the stalk of the pituitary to enter the wall of the third ventricle Nevertheless, this author is still reluctant to consider the tumours produced as truly neoplastic More recently Vazquez-Lopez (personal communication) has found that prolonged administration of stilboestrol, combined with thiourea, causes the development in rats of tumours of a more convincing malignant character

Whether oestrogens will be found ultimately to give rise to truly cancerous proliferation of pituitary glandular cells remains undecided In any case, the adenoma-like reactions found in rodents can be produced only by excessive oestrogen administration ranging over a long period of the normal life-span, comparable in humans, as Cramer & Horning (1936) have pointed out, to a period of 7 to 10 years The therapeutic administration of oestrogens therefore seems unlikely to result in the formation of human pituitary adenomata or tumours of hyperplastic origin

3 Mammary Cancer

Fifty years ago the ovaries were thought to be responsible for mammary cancer (Beatson, 1896) Since then the hypothesis has been found correct, and various workers have shown that the disease in mice can be largely prevented by removal of the ovaries in youth (Lathrop & Loeb, 1916, Loeb, 1919, Cori, 1927, Murray, 1928) Later it was learned that, if mice are spayed on the day after birth, some recovery of oestrogenic power is apt to occur, probably due to an increased formation of oestrogen by the adrenals, and although mammary cancer may follow, its incidence is reduced and the disease occurs later in life than in mice which have not been spayed (Fekete, Woolley & Little, 1941) Murray (1928, 1930) found that cancer of the breast may develop in castrated male mice into which ovaries have been transplanted, and a similar result has been reported by De Jongh & Korteweg (1935) No instance of spontaneous mammary cancer in male mice had been recognized until Athias (1945) and Athias & Furtado Dias (1941) described the occurrence in a single strain (H), and in these mice the disease is associated with an abnormality of the testes

Our knowledge advanced when it was shown that the ovarian factor in carcinoma of the breast is present in the follicular fluid of the ovary (Goormaghtigh & Amerlinck, 1930) This factor was eventually isolated from the liquor folliculi of sows' ovaries by MacCorquodale, Thayer & Doisy (1936) and identified as α -oestradiol Before this date, oestrone had been obtained in a pure form from the urine of pregnant women by Doisy, Veler & Thayer (1929) and very shortly afterwards by Butenandt (1929) working independently To-day, numerous pure oestrogenic compounds, natural and synthetic, are available for biological experiments, and every one of them which has been tested for the purpose has been found able to cause cancer of the breast in male and female mice, including oestrone (Lacassagne, 1932, Burrows, 1935), oestradiol (Gardner, Smith, Allen & Strong, 1936), Girard's equilin and equilenin (Lacassagne, 1936, Gardner, Smith, Strong & Allen, 1936), triphenylethylene (Robson & Bonser, 1938), and stilboestrol (Lacassagne, 1938) Geschickter (1939), Eisen (1942), and Nelson

(1944) have induced mammary cancer in rats with oestrone, oestradiol dipropionate, and stilboestrol.

Although oestrogen is a leading agent in causing mammary cancer, it has this effect only in the presence of other factors Many pure strains of mice are now available, in some of which—known as high-cancer or HC strains—there is a high incidence of mammary cancer in the untreated females, and in these mice the males also are apt to have cancer of the breast after treatment with oestrogen. In the other—low cancer or LC—strains, spontaneous mammary cancer is rare in the females and is not usually produced in the males by oestrogen (Lacassagne, 1933, 1935, Twombly, 1940, Bittner, 1941) The difference between these two kinds of mice is caused by the presence or absence of certain hereditary factors In this connexion it may be noted that the transplanted ovary of an LC mouse, by providing oestrogen, may induce cancer of the breast in a male, but only if he belongs to an HC strain (Little, 1936)

Hereditary Factors Required for the Induction of Mammary Cancer by an Oestrogen¹

Genic factor Though genes play some part in susceptibility to cancer of the breast in mice, the part is small, for in these animals the susceptibility is transmitted mainly through the mothers The small paternal influence is genic (Lathrop & Loeb, 1918, Cloudman & Little, 1936, Korteweg, 1936), and both Bittner (1940a), and Andervont (1940) believe this genic factor to be a mendelian dominant It is uncertain whether (Andervont & McEleney, 1941) the genic factor affects the susceptibility of the mice to the cancer-producing tendency of oestrogen or whether it controls the non-genic hereditary factor itself

Non-genic hereditary factor The predominance of hereditary factors unconnected with chromosomes is clearly shown by Little (1933), who cites the findings of four independent inquirers (Table I), displaying how little a share the paternal genes exert on the incidence of this form of cancer

TABLE I EFFECT ON INCIDENCE OF MAMMARY CANCER IN MICE OF CROSSING HIGH-CANCER (HC) AND LOW-CANCER (LC) STRAINS (Little, 1933)

Experiment	Type of cross		Percentage of mammary tumours in 1st generation of females
	Female	Male	
I	HC × LC	LC	36.06
	LC × HC	HC	5.53
II	HC × LC	LC	68.11
	LC × HC	HC	7.41
III	HC × LC	LC	86.3
	LC × HC	HC	0.0
IV	HC × LC	LC	90.0
	LC × HC	HC	0.0

Korteweg (1936) obtained similar results, his experiments show also that the occasional small increased genic susceptibility in the offspring of a low-cancer strain mother and a high-cancer strain father may be continued in the second (F_2) generation That the non-genic hereditary factor is transmitted in mice by the mothers alone has been clearly established by Murray & Little (1936), Bittner & Little (1937) and others In man the existence of this kind of factor is uncertain Wassink & Wassink van Raamsdonk (1923), Waaler (1932) and Wassink (1935) have found indications

¹[See also the paper by G. M. Bonser on the genetics of cancer, in an earlier issue (*BMB* 876) — Ed.]

of a familial tendency of this kind in man, though other researchers have failed (Passey, 1942)

We have now to consider how the non-hereditary factor is transmitted from mother to child Bittner & Little (1937) transferred fertilized ova from HC mothers into the uteri of LC mice and the tendency to mammary cancer disappeared from the young which had been treated in this way Fekete & Little (1942) on the other hand showed that LC ova transferred to HC mothers thereby acquired a special liability to cancer of the breast Moreover it has been shown that the factor is conveyed to the young in the mother's milk for HC new-born mice suckled by LC mothers acquire thereby a lower chance of getting cancer than is characteristic of their strain (Bittner & Little 1937) Such an effect however results only if the transference is done almost immediately after birth (Bittner 1939, Andervont & McEleney, 1939 1941) Furthermore, Andervont Shimkin & Bryan (1942) found that the susceptibility to this factor seems to decrease soon after birth although the factor itself remains present in the mother's milk throughout lactation (Bittner 1940b) Once the non genic factor has been eliminated from mice of an HC strain their greatly reduced liability to mammary cancer is continued in subsequent generations (Bittner 1937)

The mother's milk is not the only medium by which this factor can be transferred to the young for it can be conveyed to LC mice by implantations of tiny pieces of spleen, thymus or blood derived from an HC mouse (Bittner 1939, 1940b Woolley Law & Little, 1941)

Absence of the non-genic factor from an LC mouse does not mean that the mouse is resistant to this factor, it may in fact be very susceptible to it whereas mice of certain other strains do show a high resistance against the factor (Andervont 1940, Murray 1941)

The continuance of a susceptibility to cancer under the influence of oestrogen once it has been established by the presence of the non-genic factor, continues from generation to generation which shows that the agent multiplies in the body and that it may be a virus, its dimensions accord with such a concept (Visscher, Green & Bittner, 1942, Bryan, Kahler Shimkin & Andervont 1942)

It may be added here that the development of uterine cancer in response to oestrogen is not dependent on the presence of this non-genic factor (Allen & Gardner, 1941)

4 Uterine Fibromyomata

The experimental induction of uterine fibroids in laboratory mammals by oestrogen administration is confirmed by many authors The development of these tumours can be inhibited and in some cases prevented by endocrine therapy It is encouraging further to find that recent clinical work on the origin and treatment of this disease in women is in accord with the experimental results obtained in animals

Lacassagne (1935) found fibromyomatous changes in the uteri of rabbits and mice, following the injection of oestrogens He also noted that the reaction of the uterine stroma to oestrogens varies in degree in different strains of inbred mice Later Nelson (1937) Moricard & Cauchoux (1938) and Lipschütz & Inglesias (1938) using different oestrogenic compounds induced uterine tumours in guinea-pigs Ovariectomy, according to Lipschütz Rodriguez & Vargas (1939) accelerated the appearance of uterine fibroids in these rodents It was also found that small dosages of oestrogen were more

effective than larger ones (Lipschutz 1942) although a difference existed in the reaction of the uterus to oestrogens in different species According to Lipschutz & Vargas (1940) stilboestrol is the most potent oestrogen for the production of uterine fibromyomata in guinea-pigs

Perloff & Kurzrok (1942), by implanting pellets of oestradiol benzoate in the uteri of guinea-pigs, succeeded in further hastening the development of the tumours all of which arose at the site of implantation as early as 32 days after treatment commenced It is of interest to note that Lipschutz Inglesias & Vargas (1939) found that the tumours regressed when oestrogen treatment was terminated There is therefore a similarity between fibromyomata and the adenomata of the pituitary which arise after prolonged oestrogen administration, since the latter also regress when treatment is discontinued

Vargas (1943) demonstrated that oestrogens do not act through the pituitary in causing uterine tumours in guinea-pigs, although an indirect action of this kind does take a part in the origin of mammary cancer in mice Thus Vargas succeeded in producing experimental uterine fibroids with oestrogens in hypophysectomized animals and noted that a continuous administration of the hormone in the same rodents failed to stimulate growth of the mammary glands

That androgens or progesterone afford some protection against the tumour-producing effect of oestrogens seems likely, since Lipschutz, Vargas & Ruz (1939) found that testosterone propionate if injected in a proportion of 22:1 against oestradiol benzoate, inhibited uterine tumour formation Similar results were obtained when progesterone was given simultaneously with oestrogen.

There is a further aspect of the problem of uterine fibromata to be found in connexion with vitamin E deficiency Tumours similar to those induced by oestrogens, develop in rats kept on a diet deficient in vitamin E (see Martin & Moore, 1939, Barrie, 1938) Shute (1944) has made the suggestion that in all vitamin-E deficiencies the blood-level of oestrogens tends to rise He regards vitamin E as an anti-oestrogen.

Turning to the clinical field we find a wealth of evidence linking uterine fibroids with oestrogenic stimulation (see Tietze 1934, Witherspoon, 1935, Pineda & Porres, 1944 Austin & Ramsey, 1944, Greenblatt, 1943, Perloff, 1942, Shute, 1944) Ovarian tumours functional menorrhagia and other conditions associated with a high level of oestrogen in the blood-stream, may occur in subjects having uterine fibromata or allied conditions Regression of these tumours in women follows oophorectomy as well as the implantation or injection of testosterone propionate, just as it does in laboratory animals (see Greenblatt 1943, Perloff, 1942, Shute 1943) Similar results may be obtained according to Shute (1944), by treatment with progesterone or vitamin E

From all these observations it is clear that care must be taken with the administration of hormones affecting the uterine tissues It seems likely for instance, from the reports of Portes (1938) and Shute (1936) that prolonged treatment of dysmenorrhoea with oestrogen may lead in some cases to the development of uterine fibroids Moreover in a recent review by Scheffey Farrell & Hahn (1945) it is pointed out that the hasty diagnosis of benign uterine fibroids some of which may be actually malignant uterine tumours, is not without danger if endocrine therapy is to be employed Hormonal treatment of malignant conditions in the uterus would prove not only useless but harmful.

5 Uterine Adenomata and Carcinomata

Epithelioma of the cervix A keratinizing metaplasia of the lower terminal end of the uterus is familiar to experimentalists as a result of the continued administration of oestrogen. The condition occurs in rhesus monkeys (Overholser & Allen, 1933; and others) as well as in rodents. Experimentally, however, no unquestionable instance of cervical cancer was caused by this method in any animal until Allen & Gardner (1941) found that it could be induced in this way in mice of the CBA strain, or in crosses of this strain with C57 mice. Oestradiol benzoate in weekly doses of 16 μ g caused uterine cancers in 25 of 44 such cross-bred mice. Their observations have since been confirmed by others (Miller & Pybus, 1942), and they leave no doubt that, given suitable conditions, oestrogens may bring about epithelioma of the cervix.

Adenoma and adenocarcinoma The evidence that oestrogens may be, in part at least, the cause of uterine adenomata is mainly observational. In women, the association of adenoma and adenocarcinoma with other lesions known to be due to excessive oestrogenic action is recognized, and fibroids, polypoid adenoma, endometrial hyperplasia and carcinoma may all be associated in a single patient, and have been observed in women with certain ovarian tumours which produce oestrogen, e.g. granulosa-cell tumours.

Endometrial carcinoma is common in rabbits. Greene & Saxton (1938) reported 83 instances of this disease in their own rabbits, and Greene (1941) believes there is abundant evidence that oestrogen is a cause. One of the writers (Burrows, 1940) recorded 15 cases of endometrial cancer occurring among 25 of his rabbits, and in 3 of these cases carcinoma of the breast was present in addition. In all the affected rabbits the primary tumours were multiple, and in several of the animals malignant tumours were accompanied by seemingly innocent adenomatous polyps, and occasionally fibromyomata were present also. The ovaries of these rabbits were enlarged, yellow in colour, and consisted mainly of lutein-like cells, and the breasts not rarely were affected with cystic mastopathy. These experiences have been confirmed by later and more extended experience. The results strongly suggest that oestrogen is the main, though perhaps not the only, etiological factor in this form of malignant disease.

6. Ovarian Tumours

There are two features which suggest the possibility that ovarian cancer may be caused by some specific agent conveyed by the blood-stream. One of these is the considerable frequency with which both ovaries are affected, and the other, less striking fact, is that malignancy may become imposed on some innocent abnormalities of the ovary. Experimental work has not hitherto revealed the existence of any such specific agent. Concerning innocent tumours of the ovary, including multilocular cysts and endometriosis, it does appear that oestrogen may be regarded as a causal agent. Champy (1937) has found that a continued subjection of mammals to injection with oestrogen nearly always brings about invaginations of the germinal epithelium with the formation of multiple mucoid cysts. In the course of time, he says, papillomata are apt to develop from the cyst-walls.

While mentioning these observations by Champy, it has to be admitted that the possible causation of ovarian tumours

by oestrogen has received little substantiation in the laboratory, and a firm opinion on the subject is at present hardly justified.

7. Tumours of the Testis and Epididymis

Testis. Tumours of the testicle, like those of the ovary, are frequently bilateral, and in some instances at least, oestrogen appears to be an etiological agent. Burrows (1935, 1936, 1937) showed that under repeated cutaneous applications of oestrogen, there occurred in some mice a great increase in the number and size of the intertubular glandular cells, while the tubular epithelium gradually became eliminated. As a result the testes became enlarged, yellowish in colour, and tended to a globular shape. Though usually of unequal degree in the two testes, the condition was bilateral as a rule, and in these mice, which were non-pedigree animals obtained from a dealer, no instance of malignancy occurred. Gardner (1937), confirming these observations, found that the condition could be caused in some strains of mice more readily than in others. He gave large doses of oestrone benzoate (500 international units) or equilin benzoate (0.1 mg) once a week to mice of the following strains: Strong A, C₃H, CBA, N, F. Only in the Strong A mice was this hypertrophic condition of the Leydig tissue produced. These results were confirmed by Shumkin, Grady & Andervont (1941).

Bonser & Robson (1940), like Gardner, found that the Strong A mice were particularly susceptible to this condition. They gave the synthetic oestrogen triphenylethylene (3 mg subcutaneously once a week) to mice of the strains R III, CBA, and Strong A. Hyperplasia of the Leydig tissue appeared only in the Strong A mice, and in them the condition occasionally suggested the presence of a malignant change, metastasis being suspected in one. In a later paper Bonser (1942) states that bilateral interstitial-cell tumours developed in the testicles of every one of 8 Strong A mice which had been treated in the way just mentioned and had survived for 50 weeks. It is now well established that interstitial testicular tumours with metastases can be induced by oestrogens in Strong A mice (Hooker, Gardner & Pfeiffer, 1940; Hooker & Pfeiffer, 1942).

It may be noted that Fell (1922) recorded a comparable hyperplasia of the interstitial tissue in the scrotal testicle of a pseudohermaphrodite pig.

The writer attempted to produce tumours by injecting 0.5 mg of equilin in oil into the testes of 4 rabbits. The injections were given once a week for 34 weeks and were usually made into the right testis, but occasionally into the left if the right appeared excessively tense. Eventually one of the two survivors was killed because of a seminoma of the left testis with metastases. Possibly, in some circumstances, cancer of the testis may be caused in the rabbit, as in the fowl, by non-specific injury of the organ; other laboratory experience suggests such a possibility. Does such trauma lead the testis itself to produce oestrogen? An occasional result of injury of the testis in man is gynaecomastia, and the association is suggestive.

It may be that the malignancy which so often affects undescended testicles in man is attributable to the formation of oestrogen. Facts which suggest such a possibility are the following:

- 1 Undescended testes are apt to show a hyperplasia of the

glandular interstitial tissue like that caused in certain mice by oestrogen

ii Malignant tumours growing in the cryptorchid testes of three dogs were all accompanied by changes in the mammae and accessory reproductive organs like those caused by oestrogen (Greulich & Burford, 1936)

iii Experiments have shown that ovaries of mice implanted in the ear, where they are subjected to a lower temperature than in the abdomen, produce an excess of androgen (Hill & Gardner, 1936, Hill, 1937, 1941, Hill & Strong, 1940, Deanesley, 1938) Analogy suggests that a testis retained within the abdomen may possibly produce an excess of oestrogen

iv In a special strain of mice (H) in which spontaneous mammary cancer occurs in the males, hyperplasia of the interstitial glandular tissue, like that caused by oestrogen, is present also (Athias & Furtado Dias, 1941, Athias 1945)

Epididymis Tumours of the epididymis, such as are caused by oestrogens, do not seem to have been observed in mice or rats, though an epithelial metaplasia is an occasional sequel in the former Vazquez-Lopez (1944), however, implanted oestradiol (10 mg.) subcutaneously in 3 male hamsters 6 weeks old, and at the end of 297 and 327 days 2 of the animals had carcinoma of the epididymis, the condition being bilateral in one of the instances

8 Benign Enlargements of the Prostate

The dependence of the prostate on the testes and its atrophy after their removal, were long ago recognized by John Hunter, and at the end of the last century it was seen that even benign enlargements of the prostate shrank after castration From such knowledge it seems clear that, not only the normal growth of the prostate, but benign enlargements also of that organ are caused by gonadal hormones Experimentally it has been shown that oestrogen in excess of a normal supply causes atrophy of the secretory elements of the prostate, together with a hyperplasia of their fibromuscular stroma (Courrier & Gros 1934 1935, Van Wagenen 1935a 1935b, Parkes & Zuckerman, 1935), and the distribution of these changes suggested both to De Jongh (1935) and Burrows (1935) that the benign enlargement of the prostate in elderly men might be the result of a relative excess of oestrogen

The increase of fibromuscular tissue found in benign prostatic enlargement mainly affects that part of the gland adjacent to the uterus masculinus, whereas the lateral lobes though compressed remain relatively unaffected To explain this partition of effects it has been plausibly suggested that in man the part of the prostate which surrounds the uterus masculinus has been derived from Müllerian forerunners, whereas the main body of the gland is of Wolffian origin

Unfortunately there has been until lately no animal upon which these ideas might be conveniently tested. A remedy for this situation seems at hand, for Lipschütz Yamine Schwartz, Bruzzone Acunã & Silberman (1945) have lately found that prostatic enlargements involving fibromyomatous hyperplasia can be induced by oestrogens in the guinea-pig and that this growth can be prevented or checked by the simultaneous administration of progesterone, deoxycorticosterone or testosterone propionate

From the foregoing remarks it appears although it is perhaps not finally proved, that the benign prostatic enlargements of advancing age may be attributed to a decline in the

production of one or more of the steroids mentioned relatively to the supply of oestrogen, and that a species on which this hypothesis may be tested is now available

9 Adrenal Tumours

A relationship between the sex hormones and adrenal tumours has long been recognized but the precise role played by these hormones has been obscure Clinical evidence has shown that excessive amounts of androgenic and oestrogenic substances may be present in the urine of patients suffering from adrenal tumours (Burrows Cook Roe & Warren 1937, Butler & Marrian, 1938) Unlike mammary cancer, adrenal tumours do not normally develop spontaneously in mice It is therefore of great interest to find that Woolley & Little (1945) have recently discovered the factors necessary to induce cortical carcinomata in certain inbred strains of mice

Earlier experiments had indicated that in some inbred strains nodular hypertrophy of the adrenal cortex resulted from ovariectomy (Woolley Fekete & Little 1939) Adrenal cortical tumours were obtained by Gardner (1941) in 13 out of 15 mice of the NH strain ovariectomized at the age of 43 to 65 days These tumours were accompanied by specific changes in the accessory genital tissues and the skeleton similar to those associated with oestrogenic stimulation. Woolley Fekete & Little (1940) carried out a systematic examination of the development of adrenal and gonadal changes in different inbred strains of mice following ovariectomy They found some variation in the extent of the changes and noted that a high incidence of spontaneous mammary cancer seemed to be accompanied by more extensive adrenal cortical neoplasia and greater hyperplasia of the accessory sex organs, following ovariectomy, than occurs in mice with a low incidence of mammary cancer The most striking and consistent results were obtained however by using the CE strain of mice which has a low incidence of mammary tumours, but a high incidence of ovarian tumours When mice belonging to this strain were ovariectomized at 1-3 days after birth, 100% developed adrenal cortical carcinomata accompanied by changes in the accessory sex organs Castration shortly after birth likewise led to the formation of cortical carcinomata in 100% of the males The tumours in both sexes metastasized in many cases and were found to be transplantable No regeneration of the gonads was detected in any of the operated mice at autopsy, and no adrenal tumours developed in either the intact males or females of this strain.

The condition of the accessory sex organs, following gonadectomy in both sexes indicated that they had been subjected to the influence of sex hormones Thus the ovariectomized females showed in the uterus, vagina, clitoridean glands and mammary glands the changes associated with prolonged oestrogenic stimulation In the castrated males with adrenal tumours the seminal vesicles and prostate glands were enlarged, and in many mice squamous metaplasia of the prostatic epithelium and an increase in the hyaline connective tissue of the prostatic stroma had occurred. Woolley & Little (1945) emphasize the fact that these changes were similar to those recorded by Burrows (1935) in male mice following treatment with oestrogens Dorfman & Gardner (1944) made a biological assay of ovariectomized mice of the NH strain and discovered that the tumour-bearing ovariectomized mice secreted four times as much

oestrogen in their urine and faeces as the intact females of the same strain

Taylor & Wiseman (1942), and others, have found that neoplasia of the human adrenal cortex is more common in females. These clinical observations are probably not unrelated to the findings of Woolley & Little (1945) that ovariectomized mice develop tumours earlier than castrated male mice, and that this difference in susceptibility seems to be constant within certain strains. A further aspect of the problem has been revealed by Woolley & Little (1945) in that adrenals of gonadectomized mice, killed at varying intervals, showed the malignant changes to be related to a process of brown degeneration in the X zone. Cramer & Horning (1937) had previously called attention to the association of brown degeneration in the mouse adrenal with other forms of cancer. In view of the possible relationship between vitamin-E deficiency and abnormal oestrogenic stimulation (see section on uterine fibroids), it should be noted that Hueper & Martin (1942) found an adrenal tumour in a castrated rat fed on a diet deficient in this vitamin. There seems little doubt, therefore, that oestrogenic stimulation is associated with the induction of adrenal cortical carcinomata, and it is remarkable that, in order to induce these tumours experimentally, only two factors are necessary—the selection of a suitable strain of inbred mice and the removal of the gonads at an early age.

Since it is established that the biological activities of the gonadal and adrenal cortical hormones normally overlap (see Burrows, 1945), the one set of hormones acting in part at least as substitutes for the other, it seems likely, as Fekete & Little (1945) have suggested, that the initial growth of the adrenal cortex in castrated mice may be due to an effort on the part of the adrenal to compensate for the absence of the gonads. Whether continuous injection of either androgens or oestrogens would affect, or prevent, the formation of adrenal tumours in gonadectomized mice, does not appear to have been investigated.

10. Subcutaneous Sarcomata

Experimental evidence suggests that the sex hormones are endowed with a capacity for inducing non-specific cancer. Sarcomata of the spindle-cell and round-cell varieties have frequently developed in mice or rats, following continuous subcutaneous injections of oestrogens (Cori, 1927, Suntzeff, Burns, Moskop & Loeb, 1936, Gardner, Smith, Strong & Allen, 1936, McEuen, 1938, Burrows, 1945). Subcutaneous transplantation of these tumours, when attempted, was successful. Lacassagne (1939) appears to be the only investigator who has reported the same phenomenon following injections of testosterone propionate or testosterone acetate in mice. Tumours occurred in 35% of his animals.

In every case the sarcomata, whether induced by the male or female sex hormones, arose in the subcutaneous connective tissues near the site of injection. Gardner *et al.* (1936) were of the opinion that the sarcomata always developed at the point of contact between the tissues and the oil containing the hormone in solution. Other workers, however, have obtained the same type of tumour by the use of oestrogen in aqueous solution. As most of the injected oestrogens in these experiments were dissolved in oils, the possibility that the oil and not the hormone might possess carcinogenic properties could not be neglected. Burrows (1932), however,

has studied the effects of repeated subcutaneous injections of various oils in mice, and found that, although the tissues reacted in an inflammatory manner, no sarcomata developed. Mere mechanical injury to the connective tissue, caused by the injection needle, appears to have no detectable carcinogenic effect.

Gardner *et al.* (1936) draw attention to the fact that previous workers (Cook, Dodds, Hewett & Lawson, 1934) have shown that certain hydrocarbons, which induce cancer in mice, either when applied to the skin-surface or injected subcutaneously, have been found to possess both oestrogenic and carcinogenic activities. There is a close chemical relationship between these hydrocarbon carcinogens and oestrogenic hormones. These authors also point out that oestrogens under certain conditions may have a stimulating effect on mesodermal as well as epithelial cells.

Burrows (1945) suggests that the origin of sarcomata, arising from injection of male sex hormone, might be traced to the conversion of androgen into oestrogen inside the body. He also draws attention to the fact that continuous painting of the skin-surface of rodents with sex hormones does not lead to skin-cancer. It is interesting to note that no cases are reported of sarcomata arising after the subcutaneous implantation of oestrogen pellets. Recently Perloff & Kurzrok (1941) found that pellets of oestradiol benzoate implanted in the uteri of guinea-pigs, lead to the production of fibromyomata at the site of implantation. But this is a phenomenon arising in relation to overstimulation of tissues which normally respond to a particular hormone, and it is difficult to visualize the same sort of reaction taking place in other connective-tissue areas not specifically sensitive to normal levels of the hormone.

11. Leucaemia

Leucaemia arises either from marked hyperplasia of various forms of mature and immature leucocytes, leading to a permanent leucocytosis and the appearance of immature forms in the circulation, as well as overgrowth of the haemopoietic tissues, or, on the other hand, to a hyperplasia which may still involve mature and immature leucocytes, but with the proliferation confined to some or all of the haemopoietic centres without necessarily affecting the leucocyte population of the blood-stream. Whatever variety of leucaemic change takes place, and the change rarely involves more than one type of stem-cell, the end results are regarded as neoplastic. The fundamental aspect of the disease seems to be a partial or complete independence of the leucocyte or its precursors from the regulation of growth and differentiation.

Most of our knowledge of the factors which either induce or modify the growth of the disease has been gained from experiments on homozygous strains of mice which develop spontaneous leucaemia in varying degrees. Information, though of less importance, has also been acquired from investigations on mice and rats of mixed ancestry bearing transplantable tumours.

Avian leucaemia, which can be transmitted by a cell-free filtrate, is not included in this review, as the relationship between leucaemia and oestrogens has been investigated mainly in inbred strains of mice. It is also recognized that leucaemia in mice is a similar disease to that occurring in humans, with the exception that in most inbred strains of mice leucaemia is more prevalent in the females than in the

males. In humans the reverse is the case, the ratio being 2:1 in favour of the males. Cole & Furth (1941) contend that the differences attributable to sex, which occur in most strains of mice in relation to the spontaneous development of leukaemia, are insignificant. The problem has been examined statistically by MacDowell, Potter & Taylor (1939) who maintain that, as the females possess a higher longevity than the males, this in part explains the higher incidence of leukaemia among the female stock. Furth (1946) finds however that most males outlive their leukaemic sisters. The higher incidence in homozygous females is attributed by Furth to the presence of an endocrine factor.

Recent experiments seem to suggest that several factors such as oestrogens (Gardner, Dougherty & Williams, 1944), adrenal cortical hormone (Dougherty & White, 1943), carcinogenic hydrocarbons (Morton & Mider, 1941, Engelbreth-Holm, 1942), diet (Tannenbaum 1940), and irradiation (Engelbreth-Holm 1942), may influence the growth and behaviour of leukaemia in mice and rats. Some of these agents lead to the induction of various forms of leucocytic neoplasia ranging from general leukaemia to lymphosarcoma and Furth (1946) regards oestrogens as the most potent of the leucaemogenic agents. Recent work on the relation between leukaemia and oestrogens is not unequivocal, owing to the interaction of hereditary factors, but the available evidence strongly supports the supposition that oestrogens do play an important part in the induction of the disease (Engelbreth-Holm 1942).

Lacassagne (1937) was among the first to report the development of leukaemia and lymphoid tumours in mice after prolonged treatment with oestrogen. Gardner, Kirschbaum & Strong (1940) treated 149 mice belonging to a low-incidence strain with oestrogen. 15.4% of which subsequently developed lymphoid tumours. None of the 117 untreated mice developed lymphoid tumours. In a later series of experiments, Gardner, Dougherty & Williams (1944) increased the incidence in low leukaemia strains from 2% to 25% with oestrogen administration.

Of considerable interest are the results of ovariectomy and orchidectomy on mice belonging to strains developing a high degree of spontaneous leukaemia. Thus Miller & Pybus (1942) reported that gonadectomy in either sex, of mice belonging to the Edinburgh strain, was followed by a marked increase in the incidence of lymphoid tumours. On the other hand, McEndy, Boon & Furth (1944), working with a high leukaemic strain of mice, found that the incidence was actually lowered from 74% to 45% by ovariectomy and raised in the orchidectomized males so that 60% developed leukaemia, compared with 52% of the unoperated controls. Murphy (1944) using a strain of mice in which 88.4% of the females and 53% of males developed spontaneous tumours also found that castration in the males increased the incidence of leukaemia to 97%. Ovariectomy in this strain had no significant effect. In one group of castrated males the addition of testosterone propionate to the oestrogen treatment lowered the incidence of leukaemia to 58%.

Gardner *et al.* (1940) give further evidence of the antagonism between androgen and oestrogen. For if these hormones were combined they found that only 1 mouse in 86 developed a lymphoid tumour, whereas the incidence was 15% in mice receiving oestrogen alone.

According to some workers (Furth 1946) the male sex hormone appears to be without effect if the strain of mice

has a low incidence of spontaneous leukaemia. In mice of two mixed stocks, Dmochowski & Horning (in press) found that 59% and 70% respectively of males castrated before puberty and afterwards treated with oestrogen, developed lymphoid-tissue changes resembling lymphoid tumours, whilst in the uncastrated mice of the same stock, treated with oestrogen only 11% and 19% respectively developed tumours. No changes appeared in the control untreated mice. In the majority of cases these lymphoid changes were associated with enlargement of the spleen, liver and kidneys. The position regarding the influence of oestrogens and androgens on leukaemia is therefore still obscure. Furth (1946) contends that oestrogens are the dominant factor, whereas Murphy (1944) prefers to emphasize the inhibitory action of androgen rather than the apparent stimulation of oestrogen.

It is still more difficult to unravel the part if any played by the adrenals although Murphy & Sturm (1943) have obtained a marked increase in the incidence of lymphoid leukaemia in rats following adrenalectomy. These authors reported that the transplantation of a lymphatic leukaemia in rats resulted in 90% developing the disease if the host had been adrenalectomized 15 days before transplantation, whereas in the control unoperated rats, only 45% developed tumours.

Although it is unknown how oestrogens induce leukaemia, or whether the hormone acts directly upon the haemopoietic system or indirectly through some other organ, it must be admitted that certain similarities exist between the induction of leukaemia and of mammary cancer by oestrogen administration. With both conditions, the carcinogenic influence of oestrogen is dependent upon the genetical constitution. The irreversible changes in leukaemia and mammary cancer appear to follow quite brief periods of oestrogen treatment, after which there is a latent interval and then the neoplastic changes result in tumour formation. This latent interval may be as long as 12 months as shown by Dmochowski & Horning (in press). It would appear that, in some cases, the oestrogen had induced a permanent change in the lymphoid tissue at an early stage which fails to reveal itself until rapid, uncontrolled proliferation ensues. In fact according to Furth (1946) a greater incidence of lymphoid tumours can be obtained if oestrogen treatment is short and discontinuous than if the treatment is extended. Similarly, mammary cancer in some strains of mice arises several months after oestrogen treatment has been discontinued.

If the influence of oestrogens on the induction of leukaemia proves to be an indirect one, the implication arises that the anterior pituitary gland may be involved. Flaks, Himmel & Zotnik (1938) claim that the formation of blood-cells is to some degree regulated by a "pituitary haemopoietic hormone". Whether hypophysectomy, followed by oestrogen treatment, would result in inhibition of leukaemic changes as is the case with mammary neoplasia remains to be investigated.

12. Tumours of Bone

It has long been known that a relationship exists between the gonads and the skeleton and that sex differences are associated with bone-growth. The direct influence of oestrogens on osteogenesis has been investigated however only in recent years. In response to the injection of oestrogen new bone is proliferated in immature female and male rodents especially in the medullary cavities of the long

bones. High dosages, given for prolonged periods, cause hypercalcification, and the new endosteal bone may become so over-developed as virtually to obliterate the marrow spaces (Zondek, 1937, Gardner & Pfeiffer, 1938a, b, Sutro, 1940, Miller, Orr & Pybus, 1943). According to Andrews (1942), 98% cases of hyperostosis frontalis interna occurred in women, and were generally detected during menopause.

In the experimental field it should be noted that Zondek (1937) claims to have observed a gradient of responsiveness on the part of the skeleton to oestrogens, and that the bone changes described by Sutro (1940), and Miller, Orr & Pybus (1943) were found to be reversible. In the experiments of Gardner & Pfeiffer (1938a, b), it was observed that the overgrowth of bone was more readily induced in castrated than in non-castrated mice. Moreover, these authors were able to inhibit the response of bone to oestrogens by the injection of androgens.

The occurrence of spontaneous bone-tumours in mice of mixed stock was first reported by Murray (1908), Bashford (1911), and more recently by Brunschwig & Harmon (1933).

The primary osteogenic sarcomata, described by Murray and Bashford, continued to form bone during several generations of subcutaneous transplantation. More recently, it has been demonstrated by Pybus & Miller (1940) that, in a certain inbred strain of mice, oestrogens are capable of influencing the formation of actual bone-tumours. Working with an inbred strain of mice (Simpson A), in which the incidence of spontaneously-arising bone-tumours is 53%, these authors observed the effects of subcutaneous implantation of oestrogens. The strain normally exhibits a sex difference in tumour incidence. In females 77% of tumours occur, and these arise 2½ months earlier than in males, in which there is the much lower incidence of 29%. Burrows (1945) points out that the distribution of these bone-tumours corresponds with the graded bone hyperplasias induced in other strains, as noted by Zondek (1937) and by Gardner & Pfeiffer (1938a, b). Barrett, Dalton, Edwards & Greenstein (1944) have described a further inbred strain of mice (C3H) in which spontaneous osteogenic sarcomata arise, but bone-tumours are relatively rare and the subject requires much further study.

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quantitative point of view it is difficult to compare the activity of synthetic substances and naturally-occurring hormones in view of the differences in their chemical properties. It may be said, however, that the synthetic oestrogens

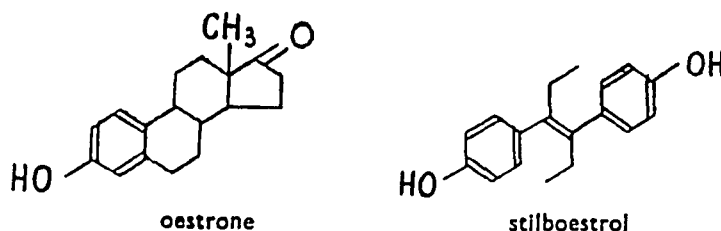
A NOTE ON THE CARCINOGENIC ACTION OF STILBENE DERIVATIVES

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The biological activity of the oestrone analogue diethylstilboestrol is now a matter of common knowledge, and it is accepted that qualitatively this compound possesses all the activities of the naturally-occurring hormone. From the

FIG 1



The formula of stilboestrol is arranged to demonstrate its similarity to oestrone

FIG 2

Compound	(Laboratory number)	Skeleton formula and carcinogen to which compound is possibly related	Number of mice		Number of tumours
			At start of experiment	After 0.1 year	
α Ethyl β sec butyl stilbene	616	 Benzpyrene	25 25 25 25	14 3 2 2	1 1 0 0
α α β Triphenyl α butylene	772	 1 2 3 4 Dibenzphenanthrene	25 25	10 9	0 0
α α Diphenyl β -ethyl- α amylene	810	 2 Methyl 3 4 benzphenanthrene	25 25	4 2	0 0
α α Diphenyl β ethyl α butylene	786	 3 4-Benzphenanthrene	25 25	5 3	0 0
α α Diphenyl β -methyl α propylene	851	 (Control to compound 786)	25 25	9 0	0 0
1 4-Distyryl benzene	795	 1 2 5 6-Dibenzanthracene	25 25	15 0	0 0

* Spindle-cell carcinoma

† Spindle-cell sarcoma

are actually more potent than the naturally-occurring hormone. The relationship between the structure of a synthetic compound and oestrone is shown by the accompanying formulae (Fig 1), and stilboestrol may be regarded as being related to oestrone if the two middle rings of this substance are opened.

It must, of course, be realized that this is merely a hypothesis, and it must be admitted that the spatial resemblance is not so striking if models made with tetrahedra for carbon atoms are compared.

It was decided to investigate the possibility of the application of this hypothesis to the carcinogenic hydrocarbons. The compounds were examined by the standard technique—painting the skin of mice with a 0.3% solution in acetone of the substances to be tested. It is interesting to note that neither stilboestrol nor hexoestrol nor the parent hydrocarbon 4,4'-dihydroxy stilbene produced any tumours. Stilboestrol, however, was found to be toxic when administered by this method, as none of the animals survived for a period exceeding 3 months, and the results therefore cannot be regarded as conclusive. The results of testing a series of analogues of carcinogenic hydrocarbons is shown in Fig 2. They show that, so far, α -ethyl- β -sec-butyl-stilbene is the only substance possessing carcinogenic activity in the series investigated. This is, however, definite, though feeble.

It is interesting to note that Professor Haddow (personal communication) investigated the activity of a number of

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EXPERIMENTAL CANCER OF THE BLADDER

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Experimental investigation of cancer of the bladder is of the utmost practical importance as there is still a considerable incidence of this disease among workers in the aniline dye industry. Although for half a century an association had been known to exist between exposure to aromatic amines and subsequent development of bladder cancer in humans it was not until 1937 that Hueper & Wolfe communicated to the American Association of Pathologists a successful attempt to induce papillary vesical lesions of benign and malignant type in female dogs receiving large doses of commercial β -naphthylamine by mouth.

Since this time several other chemicals have been found to be carcinogenic to the bladder and a stage has now been reached when a wide field is open for further experimental investigation. For not only is greater knowledge of the chemical aspect of the problem needed but also investigation of routes of entry and species-susceptibility. It is not inappropriate to state here that vigilance must be exercised in accepting as hyperplasias or neoplasms appearances which could be due to folding and tangential cutting of a normal epithelial lining.

Unsuccessful or Doubtful Attempts to Induce Bladder Tumours in Animals by means of Chemical Products from Dyeworks

The compounds most frequently tested in the early period were aniline α - and β -naphthylamine, and benzidine. They were given either by inhalation subcutaneous or intraperitoneal injection surface application or occasionally orally with the food. A few attempts were also made with such compounds as phenylene- and toluylene-diamine toluidine, 5-chloro- α -toluidine, and p -nitraniline. The experimental animals used were the rabbit, mouse, rat and guinea-pig.

These experiments have been carefully listed by Hartwell (1941) and were discussed by Berenblum & Bonser (1937) and by Hueper (1942 p 484 *et seq*). All the recorded experiments before 1937 (in which the chemical was administered at a site distant from the bladder) were completely negative, except those of Schar (1930a, 1930b) and Perlmann & Staehler (1932a, 1932b). In the case of the former, although the duration of exposure was probably sufficient, the photomicrographs of the tumours were not convincing. In the case of the latter, the period of exposure was under 12 months except in the case of one rabbit and the illustrations were no more convincing than those of Schär. The rather cautious diagnosis of "Neubildung fibro-epithelialer Natur" by three German pathologists who examined the sections independently tends to confirm this scepticism. The experiments of Berenblum & Bonser (1937) were of long duration and quite unsuccessful. Those of the workers at the Cancer Hospital Research Institute, London were varied and thorough though the exact duration is not stated in the reports. Writing in 1929 Leitch records

'For the last seven years experiments have constantly been going on with scores of chemical products from dyeworks administered by inhalation, ingestion or surface application to several thousands of animals and when the animals have died a minute examination of the urinary system has been made but no sign of neoplasia has been afforded. The solution of the problem would be welcome, for until the particular noxious substance or group of substances is known, no real measures can be taken to prevent dyeworkers cancer.'

In 1940 Mongami and Nishimura claimed to have induced bladder papillomatosis in rabbits and rats by means of subcutaneous injection of an oily solution of α -toluidine. In guinea-pigs similarly treated where the mortality was high in the early part of the experiment the early changes were seen but the animals did not live long enough to develop papillomas. No illustrations were given and the histological descriptions were very inadequate. Nagayo & Kinoshita (1940) stated that when α -naphthylamine was injected subcutaneously into rabbits guinea-pigs and rats papillomas of the bladder occurred. Kinoshita (1940), apparently referring to the same experiments mentions the papillomatosis of the bladder in guinea-pigs although so far no advanced tumour has been obtained. No details are given of these experiments and in view of the failure of other workers when using this compound they await confirmation.

Rather different in scope were the experiments of Yamazaki & Sato (1937 quoted by Hueper 1942 p 489). A watery solution of aniline (1%) was injected daily over an extended

CARCINOGENIC ACTION OF STILBENE DERIVATIVES

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these compounds with regard to their power to inhibit the growth of the Walker rat-carcino-sarcoma 256. In doses of up to 50 mg compounds 786, 795, and 851 were completely inactive. Compounds 616, 772 in 100 mg doses produced extremely slight inhibition whilst 50 mg of compound 810 produced slight but definite inhibition.

In conclusion it would appear that these substances have little

interest from the point of view of experimental cancer production, since the experimenter has the choice of a large number of compounds of an infinitely greater potency. The interest in them is therefore purely theoretical in that it does seem to support the hypothesis that simple analogues can be prepared for a number of the complex condensed carbon-ring compounds including the carcinogens.

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period into the bladders of 30 male rabbits, of which 12 showed vesical papillomas following 13 to 362 days of treatment. The papillomas were described as being situated at the apex of the organ, were stalked and covered with stratified epithelium. As several of the papillomas appeared after 13 days of treatment, the question must be asked as to whether these were true neoplasms.

[Induction of Bladder Tumours in Dogs by means of β -naphthylamine

Hueper, Wiley & Wolfe (1938) produced papillomatosis and carcinomatosis of the bladder in female dogs by daily subcutaneous and oral administration of commercial β -naphthylamine (from 300-450 mg daily in capsules) for from 20 to 32 months. The lesions observed by cystoscopy and subsequent histological examination of the bladders of 12 of the 16 dogs thus treated were identical with those seen by these authors in similar examinations of dyeworkers. The tumours continued to grow and become more numerous in some of the dogs after discontinuation of the treatment during the last 6 months of observation, while in one dog the first neoplasms in the bladder were noted several months after cessation of exposure. Although in none of the five dogs which had been killed up to the time of writing (Hueper, 1942, p. 486) was any metastatic deposit found at autopsy, in one dog there was malignant penetration into the subserosa of the vesical wall.

Bonser (1943) gave specially purified β -naphthylamine¹ by mouth to one female and three male dogs over a period of 5 years. At first, a daily dose of 150 mg was not well tolerated and was reduced to 100 mg, but after a year the dose was increased to 700 mg daily. A graded series of changes was observed in the bladder epithelium of one female and two male dogs which were treated for 3½, 4½ and 5 years respectively. The changes ranged from simple hyperplasia to anaplastic carcinoma with infiltration of the smooth muscle of the vesical wall and permeation of lymph-vessels. Metastases did not occur. The renal pelvis, ureters and urethra were free from tumours. There was evidence that the tumours had been present for some considerable time before death.

The advance of knowledge achieved by these experiments is considerable. The dog has been proved to be a suitable, though cumbersome and expensive, experimental animal. One chemical in great use in the dye industry has been found to be carcinogenic. Controversy as to whether β -naphthylamine itself or an impurity present in the commercial product is the active agent is virtually ended, for with the methods of purification used in Bonser's experiment, the amount of impurity administered to the dogs compared with the amount of β -naphthylamine administered daily (700 mg) must have been very small indeed.

Certain other facts already well-known in relation to the industrial disease have been confirmed experimentally, namely that a long induction period is necessary, that latent tumours may be present before clinical signs occur, that tumours may arise after the cessation of exposure and that local invasion is common but metastases are rare. The successful experiments have also afforded an insight into the reasons for previous failures. The large dosage required, the

long duration of administration and the choice of a suitable experimental animal were among the conditions usually not fulfilled in the earlier trials.

An urgent need at this stage is to find a small animal susceptible to this group of compounds. In view of the fact that a high incidence of bladder tumours can be induced in CBA mice with 2-acetylaminofluorene (see below), Armstrong, Bonser & Stuckland (unpublished observation) have attempted to induce bladder cancers in mice of this strain with pure β -naphthylamine administered by stomach-tube and in conjunction with various modifications of the diet. After an experimental period of 18 months or more (i.e. a period long enough for the development of 2-acetylaminofluorene bladder tumours in mice), the results have been disappointingly negative. It seems unlikely that four other strains of mice kept in the laboratory will yield more successful results.

The reasons for the species-differences are at present unknown. Such factors as the pH of the urine, habits of urination, and different modes of metabolic degradation of the compound by the liver have been discussed, without a satisfactory conclusion. The relative freedom of the rest of the urinary tract, excluding the bladder, from both the experimental and the industrial disease, is an extraordinary observation which has not yet been explained.

The mechanism by which the tumours are produced also requires further investigation. It seems possible that metabolites, rather than β -naphthylamine *per se*, may be the actual carcinogenic agents involved, but this suggestion is based on theoretical conceptions only. Various attempts to isolate metabolites from the urine of the workers or from treated dogs have led to equivocal results. A summary of possible causative mechanisms is given by Hueper (1942, p. 490 *et seq.*)

Induction of Bladder Tumours in Rats and Mice by means of 2-acetylaminofluorene

In 1941, Wilson, DeEds & Cox described the carcinogenic activity of 2-acetylaminofluorene when fed to highly inbred albino rats derived from the Slonaker Colony. Although malignant tumours were found in a number of organs, including the liver, pancreas, lung, ductus acusticus, breast and colon, the site of election was the urinary tract. Of 39 rats, treated for 95 days or more, 10 developed carcinoma of the bladder. In one of these there was also a carcinoma of the ureter and in another a carcinoma of the renal pelvis. Varying degrees of epithelial hyperplasia of the bladder and renal pelvis were noted, associated sometimes with squamous metaplasia and keratinization. Cessation of treatment at 95 days, followed by death at 266 days, resulted in the finding of a bladder carcinoma in one animal.

By contrast, Bielschowsky (1944), using albino rats, the descendants of Wistar rats, failed to find any bladder tumours in 104 animals adequately treated with the same compound. A high incidence of malignant tumours of liver, breast, ductus acusticus, intestine, uterus and skin was, nevertheless, obtained.

Armstrong & Bonser (1944) administered thrice weekly an oily suspension of 2-acetylaminofluorene by stomach-tube to mice of the CBA strain. These mice have an agouti coat, are very highly inbred, and are free from breast cancer. Of six mice which survived an adequate period of treatment

¹ The technical product used in the dye industry was distilled *in vacuo* and the distillate crystallized from petroleum ether (melting point, 110-113°C). Thus, while it cannot be maintained that traces of associated substances were not present, it seems likely that the product was reasonably pure. Tests for the presence of *p*-dinaphthylamine were negative.

(53 to 65 weeks), one developed benign vesical papillomatosis and four malignant changes in the bladder epithelium. Liver and uterine tumours were also observed.

In view of the strain differences observed in rats, it seemed important to treat various strains of mice with a view to finding the one most suitable for this type of experiment. Armstrong, Bonser & Stuckland (unpublished observation) therefore treated mice of five strains (including the CBA strain originally tested) as described above. Although bladder papillomatosis and malignant tumours were seen in all the strains tested, CBA was the most susceptible, 14 of 18 mice treated for 20 weeks or more showing bladder tumours, of which 86% were malignant. The strains could be arranged in descending order of susceptibility, the incidence of bladder papillomatosis ranging from 78% to 22%.

Induction of Bladder Tumours by means of Azo Compounds

Not only the aromatic amines (i.e. dye intermediates), but also the finished products, may cause bladder tumours in animals when given orally. Yoshida (1935) described bladder papillomas in 36 of 168 rats which survived 100 days or more of feeding with *o*-aminoazotoluol. In one rat there was a squamous carcinoma of the bladder and of the distal end of the right ureter. The photomicrographs are convincing, and 40 control animals showed no such changes, nor were parasites found in the tumour tissue or neighbourhood. Mention of this fact is necessary in assessing the origin of the bladder tumours in rats, which are commonly infested with a worm (*Trichosomoides crassicauda*), which lodges in the bladder epithelium and causes benign papillomatosis of that organ.

In the following year Otsuka & Nagao (1936) described bladder papillomas in 13 of 30 white rats fed with *o*-*m*'-dimethylazobenzol. The authors noted down-growth of epithelium into the subepithelial tissues and spindle-cell anaplasia but did not claim that any of the changes were actually malignant, although the low-power photomicrographs are suggestive. Kinoshita (1940) states that Nagao also produced bladder papillomas in rats with 4'-oxy-2,3'-dimethylazobenzol and that Nagao & Nashimoto were successful with 4'-acetoxo-2,3'-dimethylazobenzol and 4'-carbomethoxy-2,3'-dimethylazobenzol. These two latter substances were stated to be weaker than the other azobenzol compounds. No experimental details are given.

Strömbeck (1946) gave an oily solution of azotoluene by mouth to two groups of white rats, one group received an adequate diet but the other was fed on rice-flour and carrot, with consequent severe loss of weight. Although the adequately-fed group survived considerably longer than the other group (an average of 312 compared with 151 days), the bladders were normal, whereas of seven survivors of the rice-flour group, three showed metaplasia of the vesical epithelium with hyperkeratosis, three showed marked papillomatosis, and one hyperkeratosis with great epithelial proliferation but no real papillomas. Twenty per cent. of this group showed stones in the bladder.

The azo compounds have been very extensively used in the experimental investigation of cancer of the liver but no reference has been found to the production of bladder tumours by workers other than the Japanese. In view of Strömbeck's experiments, the diet of unpolished rice seems to have been an important factor in the production of the tumours. Strain differences may also have been concerned.

Cook, Hewett, Kennaway & Kennaway (1940) reported that 1,2'-azobenzene produced peculiar changes in the bladder of mice, but that no tumours were obtained. These changes were not seen in mice treated with a large series of closely related compounds.

Attempts to Demonstrate Carcinogenic Constituents in the Urine of Men and Dogs exposed to Aromatic Amines

Berenblum & Bonser (1937) collected 50 l of urine from workmen employed in a dye factory in which cases of bladder cancer had previously been reported. Three types of urinary extract were painted twice per week on the skin of 170 mice. Painting was continued for periods ranging from 18 to 40 weeks, and no tumours were obtained. Bonser (unpublished observation) and Hueper (1942, p. 486) repeated this experiment, using extracts of urine from dogs under treatment with β -naphthylamine, with the same negative results. Of the possible causes of failure, the following may be mentioned: the methods of extraction may have been unsuitable and the substances which produce tumours of the bladder may not be carcinogenic to the skin or may not have been present in sufficient quantity to produce the carcinogenic effect.

In this connexion, an experiment of Strombeck (1946) may be mentioned. In an attempt to discover whether the carcinogen acts directly on the bladder epithelium by its presence in the urine, this author transplanted a piece of bladder-wall (about a third of the organ) to the liver in 18 rats and subsequently fed the animals on a diet of rice-flour and azotoluene. Nine animals which survived 40 to 95 days of treatment showed metaplasia of the bladder epithelium, while four treated for longer periods showed papillomatosis as well. Seventy per cent. had stones in the bladder. In 16 of the 18 animals the bladder transplant survived and showed a vital, well-vascularized bladder-wall lined by low transitional epithelium and devoid of either metaplasia or papillomas. Among the 16 rats with a normal transplanted mucosa, there were three with papillomas and nine with hyperkeratosis in the rest of the urinary bladder. From these results the author concluded that the tumours were urogenous rather than haematogenous in origin.

Apart from its value in relation to the dye industry the experimental investigation of cancer of the bladder seems likely to provide an important link in the investigation of the cause of cancer in general. As pointed out by Bielschowsky (1946), the three aromatic amines 2-naphthylamine, 2-amino-fluorene and 2-anthramine have been found to induce distant tumours: the first of the bladder, the second of the bladder and a number of other organs and the third of the skin, caecum, ductus acusticus and liver but not of the bladder in the mice and rats so far tested. The carcinogenic aromatic amines are substances of relatively simple structure and the relationship between chemical structure and biological activity is fairly close. Thus they are specially suited for the study of carcinogenesis. The discovery of Cook *et al.* (1940) that 1,2'-azobenzene exerts an unusual effect upon the bladder and is an intermediary between 2-naphthylamine and 1,2,5,6-dibenzcarbazole, which is carcinogenic to the skin (Boyland & Brues, 1937) opens up another line of investigation. It has only recently been realized how complicated are the factors of species, strain and diet in conducting these experiments. Trials of various species and strains add greatly to the labour involved but are essential if progress is to be made.

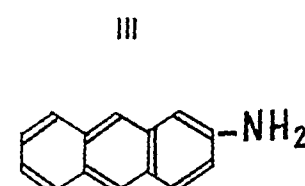
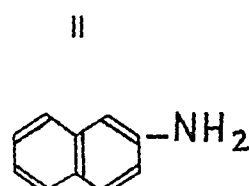
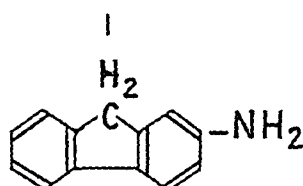
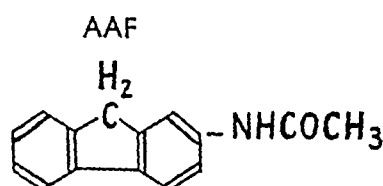
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THE CARCINOGENIC ACTION OF 2-ACETYLAMINOFLUORENE AND RELATED COMPOUNDS¹

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The great majority of the many carcinogenic substances of known constitution act at the site of application, and the compounds producing distant tumours induce carcinogenesis generally in one organ only. Fresh experimental possibilities were opened up when Wilson, DeEds & Cox described the carcinogenic action of 2-acetylaminofluorene (AAF) in 1941, introducing into cancer research an unusually versatile agent capable of producing neoplasms in many organs of every species which has been tested. Owing to 4 years of war, only a few papers dealing with AAF have been published but more can be expected in the near future. From the proceedings of medical societies and from preliminary reports published during the first 6 months of this year, it appears that several groups of research workers in Britain, as well as in the U.S.A., are actively engaged in the investigation of this carcinogen. Some of this material, the details of which have still to be published, and some of my own unpublished experiments have been included in this survey in order to make the account as comprehensive as possible. My sincere thanks are due to Drs G. M. Bonser, H. E. Harding and E. Vazquez-Lopez for their generosity and their help which enabled me to include some of their unpublished results.



¹ [The production of cancer of the kidney and bladder by 2-acetylaminofluorene is discussed in this number by G. M. Bonser (BMB 973) —Ed.]

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Chemical Configuration and Carcinogenic Activity

2-Aminofluorene (I) is an aromatic amine chemically related to two other carcinogenic amino-compounds, 2-naphthylamine (II) and 2-anthramine (III).

Aminofluorene is easily obtainable by nitration and consecutive reduction from the non-carcinogenic hydrocarbon fluorene. Its mono-acetyl-derivative is generally described as 2-acetylaminofluorene, but the term 2-acetamidofluorene is more in conformity with the nomenclature adopted by British chemists. No reference will be made to dibenzofluorene and related compounds, belonging to the group of carcinogenic hydrocarbons, but only to fluorene compounds closely related to AAF. Of these, 2-hydroxy, 2-chloro (Wilson & DeEds, 1946), 2-amino and 2-nitrofluorene have been tested adequately, and the last two substances have been found to be carcinogens. Nitrofluorene is readily reduced *in vivo* and *in vitro* to the amino-compound, the acetyl-group of AAF is easily hydrolyzable, and it seems unlikely that this group is of biological importance. One can therefore assume that the amino-group in the 2-position is essential for the carcinogenic activity. The importance of the 2-position becomes obvious when it is remembered that 2-aminonaphthalene (2-naphthylamine) and 2-aminoanthracene (2-anthramine) are carcinogens, whereas their isomers seem to be void of tumour-producing activity.

Metabolism of 2-aminofluorene and AAF

Westfall (1945) described methods for the estimation of 2-nitro-, 2-amino- and 2-acetylaminofluorene in biological material. He studied the fate of a solution of 2-aminofluorene injected into the subcutaneous tissue of a rabbit, and found only traces of the amine in the urine. A conjugated amino-compound was present in plasma and many organs, as well as in urine and bile. From this observation he concluded that aminofluorene was as rapidly conjugated as it was absorbed. Westfall mentioned that approximately 10% of the dose administered was excreted with the urine "in a combined form, that is more soluble than either

amino- or acetylamino-fluorene' Bielschowsky (1945a) isolated from rat urine a metabolite which could be identified as 2-acetyl-7-hydroxyfluorene. The solubility of this substance in water is similar to that of Westfall's conjugated water-soluble compound 2-Acetylamino-7-hydroxy-fluorene can be distinguished from AAF by its colour-reaction with nitrite, but after previous hydrolysis and diazotization it gives a weak colour-reaction when R salt is used as the coupling reagent. Recently Westfall & Morris (1946) extended their studies to rats. They found also in this species evidence for the presence of a conjugated water-soluble derivative in the urine after feeding of AAF.

The metabolite has been tested for carcinogenic activity by the writer. Five male albino rats received *per os* an amount of 2-acetylamino-7-hydroxyfluorene equimolecular to a dose of AAF, which produced malignant tumours in 42 or less weeks in more than 90% of animals of the same strain. No cancers were found at the termination of the experiment after 63 weeks.

Range of Activity

AAF incorporated in the diet has been found to be carcinogenic for 4 different species, the rat (Wilson, DeEds & Cox 1941), the mouse (Armstrong & Bonser, 1944), the fowl (Bielschowsky & Green 1945) and the cat (Harding in press). Most of the published work has been done with rodents and, as in other lines of cancer research, the use of inbred strains has already proved to be of advantage. A forthcoming paper of Armstrong, Bonser & Stickland will give the results obtained in 5 pure strains of mice. Bielschowsky (1946b) gives the distribution of tumours induced by AAF in 2 inbred strains of rats.

Dosage for Rats 1

Wilson *et al.* (1941) and DeEds & Wilson (1946) studied the effects obtained by various concentrations of AAF given to rats by mouth. The minimal effective concentration of AAF in the diet was found to be 0.004%, the maximal tolerated, to be 0.125%. This latter dose produced tumours in a remarkably short time, but the mortality was very high. In my experience a daily dose of 4 mg given for 25 weeks induced cancers in more than 90% of the animals in 42 or less weeks, when rats of age 6-8 weeks were used. Reduction of this amount to 1 mg daily per rat was accompanied by a considerable delay in the appearance of macroscopic tumours. The diet used in my experiments consisted of dry powdered bread and skimmed milk, supplemented by cod-liver oil and vegetables. As long as synthetic diets are not used, it is difficult to compare the data obtained in different laboratories, but all the available information suggests that the length of time during which the carcinogen is administered is more important than the absolute amount of AAF given.

Tumours Induced by AAF

The great majority of the neoplasms induced by AAF have been benign or malignant tumours of epithelial origin. Leukaemias have been obtained in rats in a few instances. Mesothelial tumours were rarer still. In my material of more than 500 rats, only one sarcoma was found, which like the fibroma and the sarcoma seen by Armstrong, Bonser and Stickland in mice, originated in the uterus. The single sarcoma described by Wilson, DeEds & Cox arose probably from skeletal muscle, a leiomyoma of the internal muscles of the eye was seen in one of my rats. Vazquez-Lopez (1945)

obtained one glioma in an albino rat, the first case of a malignant neoplasm of the central nervous system produced by a carcinogen administered with the food. There can be no doubt, therefore, that epithelial cells are much more susceptible to the action of AAF than mesenchymal elements or the cells of the nervous system. The number of tissues in which neoplasms have been found is astonishing. The following list shows the tumours of epithelial origin so far obtained.

Head squamous keratinizing carcinomata of the ductus acusticus externus, carcinomata of the eyelid and of the retrobulbar tissue. Most of these tumours originated from glandular structures.

Neck adenocarcinomata of the thyroid in mice and rats. Malignant tumours of this organ could be obtained in rats only in stimulated, hyperplastic thyroids.

Skin 3 basal-cell carcinomata all situated on the back were found in albino rats.

Breast mammary cancer was one of the most frequent tumours seen in the females in our strain of Wistar rats, but was rarely found in the males of this strain. Only one of 25 females of an inbred strain of piebald rats developed this type of tumour. The Leeds workers obtained mammary cancers in 2 low breast-cancer strains of mice, the incidence being higher in IF than in CBA mice.

Thorax simple adenomata and metastasizing cancers of the lung have been found in rats. In cats the lungs contained multiple foci where the cells lining the alveoli had undergone metaplastic changes and there were macroscopic nodules, in which the normal lung tissue was replaced by squamous keratinizing epithelium.

Abdomen tumours of most organs situated in the abdomen have been obtained. Benign and malignant neoplasms of the liver were the most frequent and have been found in rats, mice and cats. Tumours of the bladder or kidney have been found in all 4 species tested for susceptibility to AAF. Cancers of the small intestine, of the colon and of the pancreas were rarer. Simple papillomata of the stomach have been seen in mice on 4 occasions and carcinomata of the uterus have been found in rats and mice. One cancer of a seminal vesicle has been observed in a rat. All data referring to tumours of cats are due to the courtesy of Dr Harding, and the data on mouse tumours to the courtesy of Dr Bonser.

Mammary Cancers

As already mentioned the mammary glands of rats and of low breast-cancer strains of mice have been found susceptible to the carcinogenic action of AAF. Neither this substance nor the metabolite isolated from the urine of rats produced oestrus in rats in doses up to 100 mg, but it has been shown that the presence of the ovaries is of great importance for the development of mammary cancers. Only one of 20 female albino rats spayed at the age of 4-5 weeks, and then fed a diet containing AAF, was seen to develop a tumour of the breast.

Neither the removal of one ovary and one suprarenal nor subtotal thyroidectomy lowered significantly the incidence of mammary cancer in the albino strain of rats, probably because of the compensatory hypertrophy of the remaining glandular tissue. In albino males the incidence of breast cancer was below 10% in contrast with an incidence of 60-70% in the females. Preliminary results seem to indicate that this strain was also more susceptible to the carcinogenic action of stilboestrol than our piebald rats in which mammary

cancer was rarely produced by AAF. Such findings are suggestive of a genetically conditioned difference in susceptibility of the breast glands to sex hormones.²

There is, however, evidence forthcoming that other factors have also to be considered. It was found that the incidence of mammary cancer in the females of the susceptible albino strain became low when, instead of immature animals, rats of age 6-12 months were used. Such animals tended to become anoestrous after a few weeks' administration of AAF. However, in the few females which were 6 months old at the start of the experiment, no mammary cancers developed despite the persistence of a fairly normal cycle throughout the experiment.

It seems therefore that not only the genetic constitution but also the age of the animal are important factors in the pathogenesis of these neoplasms. Once the mammary cancers were established, the presence of the ovaries was of little importance. Six rats were spayed at a time when the breast tumours became just palpable. In every case the neoplasms continued to grow. Female albino rats which had received AAF from the 6th to the 30th week of their life could be successfully mated to produce litters which they were able to nurse, despite the presence of macroscopic tumours. When breast-cancer-bearing albinos became pregnant, the growth-rate of these tumours seemed to be increased. During lactation, however, further growth was not only frequently arrested, but in many instances, when the cancers were still of relatively small size (about 1 cm diameter), regressive changes took place, leading in 2 cases to an apparent disappearance of the tumour. However, in every case observed, tumour growth was resumed once the offspring had been weaned. Mammary cancers which had already reached a large size at the beginning of gestation did not regress.

Arrest of tumour growth during lactation has been seen by Haddow (1938) and others in females of high breast-cancer strain of mice. This phenomenon is still without adequate explanation. No effects were observed when lactogenic hormone was injected into rats bearing transplanted adenocarcinomata of the breast. Histologically nearly all the AAF-induced tumours of the breast were adenocarcinomata. Benign tumours of the mammary gland have been found only twice in my material. Invasion of the muscle and metastases occurred only when the tumours had reached a considerable size. Smaller tumours were fairly solid, containing only microscopic cysts, arising from dilated ducts or alveoli. In the larger tumours, cysts produced by central necrosis or haemorrhage were common. Malignant intraductal papillomata seemed to occur more frequently than in high breast-cancer strains of mice. Squamous metaplasia occurred only rarely, and neoplasms with a scirrhous structure were infrequent too (Bielschowsky, 1944a, and unpublished results).

Cancers of the Thyroid and Pituitary

Malignant tumours of these endocrine glands have been obtained in rats by combining the administration of AAF with intense hormonal stimulation. In several hundred rats of both sexes which received an effective dose of AAF, not a single tumour arising from cells with internal secretion has been found, but when animals received with the carcinogen

a goitre-producing agent (as allyl-thiourea or sulphaguanidine which stimulate the thyroid by means of the thyrotropic hormone) malignant neoplasms of this gland were obtained. Cancers of the thyroid could not be produced if either agent was given alone for a similar period and in similar amount. Benign multiple adenomata of the thyroid could be produced when AAF and allyl-thiourea were given simultaneously (Bielschowsky, 1944b), or by the successive feeding of the carcinogen and the goitrogen (Bielschowsky, 1945b). When the order was reversed, allyl-thiourea being given first for 18 weeks and an effective dose of AAF afterwards, only single adenomata were found. Most of these were larger, but not essentially different from the single adenomata occurring in Wistar rats after prolonged administration of allyl-thiourea.

Vazquez-Lopez (unpublished results) succeeded in producing malignant tumours of the pituitary by the combined action of stilboestrol and AAF. The extraordinary hyperplasia of the anterior lobe of the pituitary produced by natural or synthetic oestrogens in the rat has been described by many workers, but invasion of the brain has never been found to occur in this species after hormonal stimulation. Two of 12 rats into which pellets of stilboestrol had been implanted first, and which then received AAF by mouth, developed tumours of the pituitary which invaded the brain. These findings of Vazquez-Lopez indicate that AAF was able to produce malignancy in the hyperplastic pituitary.

Tumours of the Liver

In rats, mice and cats, malignant neoplasms of the liver have been produced. In rats they were very similar, both macro- and microscopically, to the cancers induced by dimethylaminoazobenzene. The influence of dietetic factors on the development of these neoplasms is still under investigation, and no conclusive results have been published so far. My own impression is that it seems more difficult to inhibit carcinogenesis induced by AAF in the liver than that induced by dimethylaminoazobenzene. It might be pointed out that the frequent occurrence of tumours arising in different organs after the feeding of AAF offers certain experimental advantages. It is not yet certain whether the dietetic factors which inhibit the development of hepatomas induced by the carcinogenic azo-compounds specifically protect the liver, or whether they are true anticarcinogens.

Carcinogenic Action of 2-Anthramine

Of the carcinogenic aromatic amines chemically related to aminofluorene, only the anthramines will be included in this article. Two of the 3 isomeric aminoanthracenes, the 2- and 9-compounds, have been tested so far, the 1-anthramine being still under investigation. The 9-anthramine was found to be inactive (Bielschowsky, 1946). The carcinogenic activity of 2-anthramine was discovered by Shear (1938), who found that subcutaneous injection of a saturated solution of 2-anthramine in lard filtrate produced multiple hepatomas in "market" albino female mice. Males of the A strain were not affected.

Details of Shear's experiments were included in a recent paper (Bielschowsky, 1946a), which described the effects of 2-anthramine in 2 strains of rats, the skin of which was painted with a solution of this substance in acetone. It was found that 3 different types of tumours of the skin developed

² [Reference should also be made to a review of the genetics of cancer by G. M. Bonser (BMB 376)—Ed.]

THE PRODUCTION OF LIVER TUMOURS BY AZO COMPOUNDS

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The production of carcinoma of the liver by an azo compound was first announced by Yoshida in 1932 and a detailed description was published by Sasaki & Yoshida (1935). In these experiments *o*-aminoazotoluene (4'-amino-2,3'-azotoluene) was the substance used, and the tumours occurred in rats. They were shown to be transplantable within the same species (Ikubo 1935). The observation was confirmed by numerous workers and positive results were also obtained in mice amongst others by Shear (1937) who gives a convenient review of the history of the earlier work which followed Fischer-Wasels' demonstration of the cell growth-stimulating properties of scarlet red.

It was later shown that *p*-dimethylaminoazobenzene (butter yellow, dimethyl yellow) was more rapidly effective in rats (Kinosita 1937), though at that time success was not obtained with other species. Many other related compounds were tried and the position at different times is summarized in the reviews of Cook & Kennaway (1938, 1940). Hartwell (1941) gives a list of azo compounds which had been tested for carcinogenic activity up to that date, positive results had been obtained with acetyl-*o*-aminoazotoluene (unconfirmed by some workers), diacetyl-*o*-aminoazotoluene, methyl red, 4-oxalylamino-2,3'-dimethylazobenzene and 4'-succinoylamino-2,3'-dimethylaminoazobenzene but none of these appears to have been as potent as *o*-aminoazotoluene and *p*-dimethylaminoazobenzene.

Since Hartwell's symposium the following have been found active: *m*'-methyl-*p*-dimethylaminoazobenzene¹⁴, *p*-mono-methylaminoazobenzene^{15, 16}, *o*'-methyl-*p*-dimethylaminoazobenzene¹⁴, *p*'-methyl-*p*-dimethylaminoazobenzene¹⁴, *p*-aminoazobenzene¹⁴, 4'-methyl-4-aminoazobenzene¹⁶, 2,4'-dimethyl-4-*N*-dimethylaminoazobenzene¹¹ and 4'-hydroxy-2,3'-azotoluene¹⁷, in approximately descending order of potency, the second substance being comparable with *p*-dimethylaminoazobenzene. Interest has naturally been aroused in the possibility that azo dyes used in colouring foodstuffs might be carcinogenic but investigations in this direction have so far proved negative^{18, 19}.

Cook, Hewett, Kennaway & Kennaway (1940) tested a group of azo compounds of less closely related chemical structure, and found that 2,2'-azonaphthalene and its reduction-product 2,2'-diamino-1,1'-dinaphthyl induced new growth mostly of cholangiomatous type, in the livers of mice while 1,1'-azonaphthalene had very little such action and 1,2'-azonaphthalene appeared to be inactive.

Up to the present, however, the substances on which the most detailed investigations have been made are *o*-aminoazotoluene (AAT) and *p*-dimethylaminoazobenzene (DMAB), and it is with these that we shall be mainly concerned.]

Species and Strains

AAT gives rise to liver tumours in rats and mice. It produces cirrhosis but not tumours in rabbits²⁰. DMAB is more rapidly effective than AAT in rats, but has a very low potency for mice, though it is not quite inert^{20, 21}, no success has been reported with other species.

Law (1941) found that AAT hepatoma in mice was more readily produced in the DBA strain than in the C57 strain. Andervont and his collaborators^{1, 2, 3} found that AAT injected as a solution in olive oil or as a suspension in glycerol or added to the food, was much more effective in females than in males for various pure strains and hybrids tested.

Effects of Diet

Much work has been done on the increase or reduction in incidence of tumours (usually in rats) resulting from the

CARCINOGENIC ACTION OF 2 ACETYLAMINOFLUORENE AND RELATED COMPOUNDS

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after prolonged painting. The most malignant of these were spindle-cell tumours which could be easily transplanted. Histologically they resembled sarcomata. Besides the spindle cells, mono- and polynuclear giant cells were present, and so was an argentophile reticulum. The smaller tumours of this type were covered by an intact and hyperplastic epidermis. Basal-cell carcinomata were found 3 times in albino and once in piebald rats. Papillomata, similar to the so-called warts produced by carcinogenic hydrocarbons in mice, were seen in both strains. The skin of the Wistar rats seemed to be more susceptible, the

tumours developing in 180-260 days at the site of application. In the piebald rats malignant tumours of the skin were not seen before the 280th day, but in this strain a few distant cancers were found also. Two of these were squamous keratinizing carcinomata of the ductus acusticus externus. Such neoplasms occurred very frequently in the piebald rats after feeding AAF. Kon, Harris & Haddow (in press) obtained the same type of tumour with aminostilbenes. That 3 aromatic amines can produce cancers of the ductus acusticus externus seems of interest, since such tumours were not known to occur before this group of chemical compounds had been tested for carcinogenic activity.

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presence in the food of various factors. It is not easy to interpret the results which have been obtained. Much seems to depend on the time chosen to terminate the experiment and assemble the data. When tumours begin to occur there is a tendency for a considerable number to appear within a short space, so that a few weeks may make the difference between an apparently significant result and a negative one. Some workers have tried to avoid this source of error by doing preliminary laparotomies and killing the animals at a later date. Another difficulty is the not infrequent doubt as to whether a given lesion is a tumour or not, to which Stewart (1941) has referred, and which may lead to appreciable error in interpretation, especially in a small experiment.

It seems, however, to be established that the addition of liver to the diet inhibits production of liver cancer by both AAT and DMAB^{43 39 38 36 59}. Of various animal tissues tested, kidney was the only other dietary supplement having this effect³⁸.

Amongst the cereals, rice appears to favour the production of tumours. Maisin, Pourbaix & Cuvelier (1939) claimed to have prevented the development of cancer by the use of a diet of rye, the one DMAB tumour seen after 220 days in 148 rats having been associated with *Taenia crassicolis* (a carcinogenic tapeworm), but it now seems possible that this may have been a delay rather than prevention, in view of the results of Ando (1940, 1941) with wheat. The latter also failed to get tumours with barley, but survival of animals was poor. Morigami & Kasiwabara (1941) observed no cancers in millet-fed rats treated with DMAB when all rice-fed controls showed cancer, but here again a delaying effect cannot be excluded, as their experiment ended at 165 days. Orr (1940) observed no difference in the incidence of tumours in rats fed on mixed wheat, maize and oats, as compared with those fed on unpolished rice. A very striking inhibition was obtained by Vassiliadis (1940) with wheat flour, no AAT tumours having appeared after 2 years, this protection by wheat flour persisted even if there was rice in the diet. It seems possible that wheat flour may offer greater protection than the whole grain, as Orr & Stickland (1941) failed to obtain tumours with DMAB after 15 months, using a diet of bread. It has been stated by Opie (1944a), who gives a good account of previous dietary investigations, that the presence of rice in the diet actively favours carcinogenesis, notwithstanding other constituents. The adjuvant effect of rice has been attributed to an antioxidant which preserves the dye in the diet and intestine¹⁷.

Yeast delays the appearance of cancer and cirrhosis, but the magnitude of the effect described varies with different groups of observers^{43 57 36}. Sugiura & Rhoads (1942), who had claimed (1941) that 15% of brewer's yeast in the diet completely inhibited the production of cancer and cirrhosis by DMAB, found that cirrhosis which had already developed could be successfully treated with a rice diet containing 15% of yeast, this observation does not appear to have been confirmed. The effect of yeast, and to a lesser degree that of rice-bran, has naturally led to numerous investigations of the vitamin-B factors.

Nakahara, Mori & Fujiwara (1939) found no effect from various vitamin-B factors given separately or together. Miner, Miller, Baumann & Rusch (1943) carried out a systematic experiment with highly purified diets, in which the amounts of riboflavin, thiamin, pyridoxin, pantothenate, nicotinic acid and choline were varied. When all B vitamins were fed in moderate amounts adequate for maintenance, the

incidence of tumours was low, when all were raised to a much higher level, the tumour incidence was substantially increased. When each vitamin was reduced in turn, the others being kept at the high level, it was found that the incidence of tumours was greatly lowered when pyridoxin was reduced or omitted. Large amounts of pyridoxin fed to resistant rats tended to increase the incidence of tumours. Large amounts of riboflavin completely prevented tumours, during the period of the experiment, in rats receiving only 12% of casein in the diet. An inhibitory effect by riboflavin has also been found by others^{22 6 32}, though the effect appears to be a small one, and according to Kensler, Sugiura, Young, Halter & Rhoads (1941), depends on the simultaneous presence of adequate casein. Kline (1943) found that *p*-aminobenzoic acid reduced the incidence of cirrhosis but not of cancer. Guanidoacetic acid, nicotinamide, and choline did not alter the incidence of cancer (Miller & Baumann, 1946).

Opie (1944a) found that fat in the diet accelerated the appearance of hepatic tumours, though Nakahara *et al* (1939b) had observed no effect with added butter. Miller, Kline, Rusch & Baumann (1944) showed that the substitution of hydrogenated coconut oil for corn oil reduced the incidence of DMAB tumours in rats of 6 months, an effect which persisted when the rats received in addition pyridoxin and/or ethyl linolate. Hydrogenated coconut oil also reduces the carcinogenicity of *p*-monomethylaminoazobenzene³². Gyorgy, Tomarelli, Ostergard & Brown (1942) had stated that unsaturated fatty acids destroy *p*-dimethylaminoazobenzene *in vitro*, and suggested that the "procarcinogenic" effect of butter fat was due to the low supply of unsaturated acids, a view which would seem to be refuted by the results with hydrogenated coconut oil.

According to Opie (1944a), a diet with low protein-content favours cirrhosis, and hence increases tumour production, but Nakahara *et al* (1939b) reported no effect from fish protein. Kensler *et al* (1941) obtained an insignificant protection with casein, unless riboflavin was present, as already mentioned. E C Miller, Baumann & Rusch (1945) reduced the incidence of tumours by increasing casein from 12 to 48% in the diets, provided that the pyridoxin level was low. Sugiura (1944) obtained partial inhibition with dried whole milk, with which he claimed also to have treated liver cirrhosis successfully. Kline, Miller & Rusch (1945), using rats which were given a sub-protective level of riboflavin, found that the incidence of tumours was decreased when casein was replaced in the diet by egg-white, supplemented by biotin in order to prevent biotin-deficiency.

As regards amino-acids, White & Edwards (1942a), but not Mori (1941), found that a high cystine-content accelerated hepatic carcinoma. White & Edwards (1942b) subsequently stated that methionine had an effect similar to that obtained by them with cystine, and that the latter is not antagonized by the further addition of choline, the number of animals in the experiment was, however, rather small.

Pathogenesis

The early Japanese workers regarded the essential effect as one of progressive hyperplasia, starting in the periportal liver cells and increasing and spreading until cancer supervened. Subsequent workers^{12 16 47 15 14 46}, however, have been impressed with the importance of degenerative and regenerative changes, the most important gross evidence

being the frequent association of cirrhosis which has been emphasized by many authors. At the same time, it is undoubtedly true that tumours have often been found in non-cirrhotic livers and that, although cirrhosis can be induced by DMAB in rabbits, cancer has not been seen in this species¹⁴. In this connexion Opie (1944b) has pointed out that the regenerative type of hyperplasia of liver cells and bile-ducts may occur in the absence of cirrhosis. Further there appears to be little doubt that cancer can emerge at a stage when the cirrhosis is still reversible.

Whether cirrhosis is or is not a necessary preliminary there appears to be no doubt that the yield of tumours is greater when it occurs. The broad general view which has emerged is that proliferative changes of the type associated with regeneration are found at an early stage in treatment being more conspicuous at first in the form of new-formed bile-ducts. As this change proceeds, there is a gradual replacement of the normal architecture of liver by regeneration nodules and the formation of trabeculae of fibrous or granulation tissue which contain bile ducts of increasingly atypical structure. The appearances of the latter may be such as to cause doubt as to whether the lesions are in fact neoplastic. Macroscopically the liver becomes granular shows thin-walled cysts containing clear fluid and solid tumours which vary greatly in colour and consistency. The granularity may recede under suitable circumstances but the cysts and tumours are permanent.

Histology of Tumours

The cysts are lined by cubical or somewhat flattened epithelium and are generally regarded as cystadenomata arising from the bile-ducts. Most authors attribute the solid tumours to two sources: the cells of the hepatic parenchyma (liver-cell carcinoma or hepatoma), and the bile-duct epithelium (bile duct carcinoma or cholangioma). This was the view of the present author⁴ but it was challenged by Edwards & White (1941) who denied that a bile-duct carcinoma occurred. They claim that Orr described as carcinoma that which was actually non-neoplastic bile duct proliferation though many such lesions have an undoubted tumour type of metabolism¹⁵. But in addition to this they appear to have misunderstood Orr who did not suggest that all adenocarcinomata were of bile duct origin and they have quoted from his paper a passage from which they infer that he regarded certain tumours as of bile-duct origin though the actual quotation begins by stating that it is liver-cell tumours which are under consideration. In point of fact there does not appear to be any doubt that liver-cell carcinoma may assume a tubular structure, as Dalton & Edwards (1942) have shown by cytological evidence. On this point therefore the difference of opinion postulated by Edwards and White does not exist.

There remains the question of whether there is a bile-duct carcinoma. Stewart (1941) has argued that if it is so, it should also appear in the extrahepatic bile-ducts or even in the gall bladder (the latter presumably in the mouse as the rat has no gall-bladder). But this view is necessarily tenable only on the assumption that the action is a direct one on the parent cells themselves and not on the liver as a whole. Cameron, Kopac & Chambers (1943) have shown in tissue cultures that liver cells are much more sensitive to *N,N*-dimethyl *p*-phenylenediamine than is bile-duct epithelium and that there is a similar difference between the

tumours, this is, as they say strong evidence in favour of the existence of a bile duct carcinoma. Opie (1944b) recognizes trabecular hepatoma, adenohepatoma, cholangioma and cystadenoma.

The detailed histology of the tumours is described in the papers mentioned^{17, 18, 19}. An interesting point is that none of the tumours contains histologically demonstrable glycogen even when it is abundant in the surrounding parenchyma. Chemical estimation showed that it remains very low in transplanted tumours¹¹.

Metabolism of Induced Liver Tumours

Nakatani, Nakano & Ohara (1938) found that induced liver tumours exhibited the high rate of anaerobic glycolysis and considerable aerobic glycolysis characteristic of malignant growths in general. They also described a progressively increasing rate of anaerobic glycolysis of the liver during the stages preceding the appearance of tumours. Orr & Stickland (1941) confirmed the former observation but not the latter. They made the interesting discovery that in the glycolytic activity of tumours the substrate involved is glucose whereas normal liver cells utilize glycogen and do not attack glucose. This property of the tumours was established for growths of unequivocally liver-cell (as opposed to bile-duct) origin, and represented one of the few cases in which it had been possible to demonstrate directly a qualitative functional difference between tumour cells and the corresponding normal cells.

The fact that glucose-breakdown replaced glycogenolysis in the tumours was confirmed by Dickens & Weil-Malherbe (1943). They also investigated several highly-specialized functions of hepatic cells in the tumours and found that the following were entirely, or almost entirely lost: the formation of urea from ammonia or from β -alanine and of acetoacetic acid from caprylic acid, the oxidation of uric acid, and the synthesis of fermentable carbohydrate from pyruvic acid. Their paper includes a comprehensive review of the literature on metabolism up to that time.

Woodard (1943) showed that the alkaline β glycerophosphatase activity of DMAB tumours averaged 10 times that of normal rat liver. Cohen (1945) found that, in rats receiving DMAB the liver showed a progressively-decreasing glyoxalase activity, tumours and their transplants showed about 10% of the glyoxalase activity of normal liver.

Mode of Action

Various split products of DMAB have been isolated from the urine (Stevenson, Dobriner & Rhoads, 1942), and some of these have been shown to be toxic to various enzyme reactions e.g., a diphosphopyridine nucleotide system²¹ carboxylase²² and a sulphhydryl-containing enzyme (urease)²³. None of the metabolites so far tested is itself carcinogenic. Kuhn & Beinert (1945), following up the work of Kensler *et al* (Kensler, Dexter & Rhoads, 1942; Kensler, Young & Rhoads, 1942) have investigated a number of oxidation products of *p*-phenylenediamine (a metabolite of DMAB) and found that *p*-benzoquinone is the most active in inhibiting carboxylase. They postulate that through the special affinity of carcinogenic azo dyes, or their reduction and cleavage products for certain tissue elements in the animal body *p*-benzoquinone is continuously renewed at such sites though it may not reach them when *p*-benzoquinone itself is administered. In support of this hypothesis that *p*-benzoquinone is

the operative substance, they recall that Takizawa produced tumours in mice by painting them with it Kirby (1945b) has drawn attention to a sharp divergence between AAT and DMAB on one hand, and azonaphthalenes on the other, their tendencies being to produce liver-cell and bile-duct tumours respectively, and he argues from this that it may be

that metabolism of azo compounds to "benzidine type" derivatives favours bile-duct proliferation, while "reductive fission" favours liver-cell cancer Interesting as such hypotheses are, it is of course necessary to approach them with caution, in view of the difficulties of establishing some of the fundamental facts

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OCCUPATIONAL CUTANEOUS CANCER ATTRIBUTABLE TO CERTAIN CHEMICALS IN INDUSTRY

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- 1 Nature of the disease
 - 2 Site of election
 - 3 Causal agents in relation to occupation
 - 4 Time elapsing from beginning of employment to manifestation of the neoplasm
- Select bibliography

Percival Pott pointed out as early as 1775 that cancer on one particular cutaneous site, namely the scrotum, could be attributed to soot. Others, including Butlin in 1892, showed that the same site might be affected by other products, and it was also observed that other cutaneous sites in addition to the scrotum might similarly be affected by certain chemicals such as pitch, tar or mineral oil. Nevertheless, it was not until 1907 that it was recognized officially in Britain that cancer of any cutaneous site could be caused by pitch tar,

or tarry compounds. In this year, the definition '*scrotal epithelioma occurring in chimney sweeps and epitheliomatous cancer or ulceration of the skin occurring in the handling or use of pitch, tar or tarry compounds*' was added to the third schedule of the Workmen's Compensation Act.

Seven further years elapsed before 'Bitumen, mineral oil or paraffin or any compound or products or residue of any of these substances' were included, in 1914 in the definition in the third schedule, purely for the purpose of compensation, which was not restricted merely to factory workers.

Six further years elapsed until, on 1 January 1920, there was added to the list of diseases *notifiable* to the Chief Inspector of Factories, under Section 73 of the existing Factory & Workshop Act (now Section 66 of the Factories Act, 1937) the definition "*Epitheliomatous ulceration or cancer of the skin due to pitch tar bitumen, paraffin or mineral oil or any compound or residue of any of these substances or any product thereof contracted in a factory or workshop*". The primary purpose of this addition was the investigation as to where the disease occurred and the devising of preventive measures.

It will therefore be observed that the number of cases accepted is limited to those arising from premises as defined in the Act as factories and that there is a number of similar cases occurring in individuals not embraced by the Act, such as roadmakers, unless they spend part of their time working in a depot under the Act.

Further, it will also be observed that arsenic is not included in the definition as it has so far been considered that a case of cutaneous cancer arising from the use of this chemical in industry can be notified, as occasionally it has been, under the heading of *Arsenical Poisoning* which has been a notifiable disease since 1896, and can be interpreted to include cancer on other sites than the skin as for instance the lung should excessive incidence be sufficiently proved. Be that as it may

GLOSSARY OF UNFAMILIAR INDUSTRIAL TERMS

Blowing room	a room in a cotton mill where the cotton fibres, after unpacking are separated by a machine	Proofer	one who weatherproofs fabric or material with creosote oil
Brattice cloth	stout tarred cloth to be used for partitioning or shaft lining in a mine, the partition being known as a brattice	Pugman	a man operating a pug-mill, which is a machine for kneading and mixing materials, e.g. pitch and coaldust
Carding	a term applied to the further opening out and straightening of the cotton fibres	Ring doubling and ring-spinning	processes in which the cotton yarn is doubled or spun and guided on to the bobbin by means of a ring
Cop	the mass of thread as wound directly upon a spindle on a mulespinning machine	Roller	a term applied to a machine for rolling metal plate or to the man who operates the machine
Cotton twiner doubler	one who doubles the cotton yarn on a machine known as a twining mule	Screenman	a man who operates a screen, i.e. a sieve
Doubling	the process of twisting together two or more single yarns	Spindle moulder	a wood working machine on which the surface of the wood is moulded
Fettler	one who keeps machinery in free order in a woollen cardroom	Sponge cloth	coarse cloth of open texture as used for cleaning machinery and fire-arms
Firebeater	a fireman or stoker	Tar "pan"	a vessel in which tar is boiled
Hackle	a comb for splitting and combing fibres of flax, hemp or jute	Tenter	attendant
Nightsoilsman	a man who collects nightsoil i.e. excrement	Wharfinger	an owner or manager of a wharf
Pavior	one who paves road surface	Winding-room	a room in which the winding of cotton yarn is done
Platelayer	one who lays keeps in order, and renews the plates on a tramway or railway hence, a man employed in fixing and keeping in order the permanent way of a railway	Willey, willow	a revolving machine of a conical or cylindrical shape armed with spikes for opening and cleaning wool cotton and flax
		Willeyer willower	one who tends the above machine

TABLE I
ANALYSIS OF 3,753 CASES OF CUTANEOUS EPITHELIOMATA NOTIFIED FROM 1920 TO 1945 INCLUSIVE, IN
RELATION TO TRADE OR MANUFACTURE, AND TO CAUSAL AGENT

The letter R with attached numeral denotes the number of rodent ulcers included in the larger number (the incidence of rodent ulcer being 2.4% of the total number of cases)

TRADE OR MANUFACTURE	No of cases	No of persons	No of sites	SITES									CAUSAL AGENT
				Head and neck	Upper limb	Lower limb	Trunk	Groin	Penis	Clitoris	Scrotum	Vulva	
Cotton—Males Females	1 372 17	1 313 17	1 402 17	165R ¹ 3	233R ¹ 9	96R ¹ 1	10R ¹ —	18 —	23 —	— 1	857R ¹ —	— 3	} Mineral oil
Tar-distilling	939	538	1 001	542R ¹	270	5	6	1	8	—	169	—	
Patent fuel	610	364	640	458	65	7	4	2	5	—	99	—	Pitch
Coal gas " (ex cotton mulespinner)	319 5	305 4	331 5	138R ¹ 1	88 2	5 —	2 —	1 —	13 —	—	84 2	— —	Tar (and pitch) Mineral oil and tar
Coke-ovens	98	91	113	44R ¹	17	—	3	2	2	—	45	—	Tar (and pitch)
Oil refining shale other mineral oil	52 4	42 4	53 4	4 1R	30 1	4 —	— —	— —	— —	— —	15 2	— —	Shale oil Mineral oil
Pitch-loading (wharves)	54	36	55	22	1	—	—	—	—	—	32	—	Pitch
Metal working (ex mulespinner) (pipe dipper)	40 9 1	40 9 1	40 9 1	9R ¹ — 1	9 1 —	1 — —	— — —	— — —	— 1 —	— — —	21 7 —	— — —	} Mineral oil Tar
Electrical equipment	29	24	34	17	8	—	1	—	—	—	8	—	
Cable manufacture Cable laying (ex mulespinner)	23 2 1	22 2 1	23 2 1	4 — —	12 1 1	— — —	— — —	— — —	— — —	— — —	7 1 —	— — —	} Tar ? Oil and tar
Creosoting timber Storage of creosote	14 9	14 8	15 11	5R ¹ 3R ¹	7 6	— —	— 1	— —	— —	— —	3 1	— —	
Road construction Manufacture of road macadam of road asphalt	13 8 1	12 8 1	15 8 1	7 3 1	5 4 —	— — —	— — —	— — —	— — —	— — —	3 1 —	— — —	Tar Tar Natural bitumen
Net fixing	18	17	21	7	8	1	—	—	—	—	5	—	Tar
Producer gas	17	15	17	—	1	—	—	—	—	—	16	—	Tar
Optical lenses	16	11	17	7	8	—	—	—	—	—	2	—	Pitch
Bricks Sanitary pipes Pottery (crucibles)	10 3 1	10 3 1	11 3 1	— — —	3 1 —	— — —	— — —	— — —	1 — —	— — —	7 2 1	— — —	Creosote oil Tar Creosote oil
Coal-carbonization	11	7	11	1	—	—	—	—	—	—	10	—	Tar
Oil gas shale (ex mulespinner) Carburetted water gas	6 1 4	6 1 4	6 1 4	1 — 2	2 — 2	— — —	— — —	— — —	— — —	— — —	3 1 —	— — —	} Tar from oil
Proofing of fabric	9	7	9	2R ¹	6	—	—	—	—	—	1	—	
Wool and worsted	6	6	6	3R ¹	—	—	1	—	—	—	2	—	Mineral oil
Synthetic dyes	5	5	5	3R ¹	2	—	—	—	—	—	—	—	Anthracene
Repair of vehicles (wheelwright) " (engineer, fitter) (ex mulespinner)	1 2 1	1 2 1	1 2 1	— 1 —	— — —	— — —	— — —	— — —	— — —	— — —	1 1 1	— — —	Tar Mineral oil Mineral oil
Repair of boats and barges	3	3	3	—	2	—	—	—	—	—	1	—	Tar
Ropes (machinist) (machinist female) (ex mulespinner)	1 1 1	1 1 1	1 2 1	— 1 —	1 — —	— — —	— — —	— — —	— — —	— — —	— — 1	— — —	? Wood tar and mineral oil Mineral oil Mineral oil
Woodworking including main tenance	3	3	3	—	—	—	—	—	—	—	3	—	Mineral oil
Coal mining (maintenance)	2	2	2	1	—	—	—	—	—	—	1	—	Mineral oil
Paints (bitumastic) Painting (bitumastic)	1 1	1 1	2 1	1 1	— —	— —	— —	— —	— —	— —	1 —	— —	? Tar ? Tar
Bolting (camel hair)	1	1	1	—	—	—	—	—	—	—	1	—	Mineral oil
Brewing (maintenance)	1	1	1	—	—	—	—	—	1	—	—	—	Mineral oil
D disinfectants	1	1	1	1	—	—	—	—	—	—	—	—	Creosote oil
Firelighters (ex mulespinner)	1	1	1	—	1	—	—	—	—	—	—	—	Mineral oil and ? creosote oil
Haulage	1	1	1	—	—	—	—	—	—	—	1	—	Pitch and tar
Jobs	1	1	1	—	—	—	—	—	—	—	1	—	Mineral oil
Matches (oil storeman)	1	1	1	—	—	—	—	—	—	—	1	—	Mineral oil
Sails (ex fisherman)	1	1	1	1	—	—	—	—	—	—	—	—	Tar and ? sun rays

TABLE I (continued)

TRADE OR MANUFACTURE	No. of cases	No. of persons	No. of sites	SITES									CAUSAL AGENT
				Head and neck	Upper limb	Lower limb	Trunk	Groin	Penis	Clitoris	Scrotum	Vulva	
Clay pigeons	1	1	1	1	—	—	—	—	—	—	—	—	Pitch
Males, Total	3 735	2,957	3 902	1 453 ^a	798 ^a	119 ^a	28 ^a	24	54	—	1 421 ^a	—	
Percentage			100	37.2	20.4	3.0	0.7	0.6	1.3	—	36.4	—	
Females, Total	18	18	19	4	10	1	—	—	—	1	—	3	
Percentage			100	21.0	52.6	—	—	—	—	—	21.1	—	
Males and females, Total	3 753	2,975	3 921	1 462 ^a	808 ^a	120 ^a	28 ^a	24	54	1	1 421 ^a	3	
Percentage			100	37.3	20.6	3.0	0.7	0.6	1.3	0.02	36.2	0.07	

a committee of the Medical Research Council is at present deliberating on the question of the relationship of arsenic to cancer and, as this subject is discussed elsewhere¹ in these columns, I shall not refer further to it.

Up to the end of 1945, as will be seen from the Chief Inspector's Annual Reports, 3,753 cases in 2,975 persons

¹ [See B4B 977—Ed.]

have been notified, and their annual distribution is shown in Graph 1, this paper is based mainly on the analysis of these figures (Table I) and the knowledge gained by personal investigation inside and outside the factory.

Pitch, tar or tar-products were held responsible for 2,229 (or 59.4%) of the 3,753 cases, shale oil, mineral oil, or bitumen for 1,515 (or 40.3%), while in 9 cases the workers

TABLE II

PERCENTAGE OF EACH SITE AFFECTED IN RELATION TO OCCUPATION, AND THE CHEMICAL CONCERNED

The figures in bold type denote site of election, but in some cases the percentage is based on too small a number to be significant.

CAUSAL AGENT	TRADE OR MANUFACTURE	EXPOSED SITES					COVERED SITES					NUMBER OF SITES
		Head and neck	Upper limb	Total	Lower limb	Groin	Trunk	Vulva or clitoris	Penis	Scrotum	Total	
Pitch	Patent fuel	71.3	10.1	81.7	1.1	0.3	0.6	—	0.8	15.4	18.2	640
	Pitch-loading (wharves)	40	1.8	41.8	—	—	—	—	—	53.1	53.1	55
	Electrical equipment	50	23.5	73.5	—	—	2.9	—	—	23.5	26.4	34
	Optical lenses	41.2	47	88.2	—	—	—	—	—	11.7	11.7	17
	Total pitch	67.6	10.9	78.5	0.9	0.2	0.6	—	0.6	18.8	21.5	746
Tar	Cable-making and laying	16	52	68	—	—	—	—	—	32	32	25
	Net fixing	33.3	32.1	71.4	4.8	—	—	—	—	23.8	23.6	21
	Proofing of fabric	22.2	66.6	88.8	—	—	—	—	—	11.1	11.1	9
	Making of roads and road material	43.5	39.1	82.6	—	—	—	—	—	17.4	17.4	23
	Oil gas	30	40	70	—	—	—	—	—	30	30	10
	Producer-gas	—	5.9	5.9	—	—	—	—	—	94.1	94.1	17
	Coal-carbonization	9.1	—	9.1	—	—	—	—	—	90.9	90.9	11
	Other	33.3	25	58.3	—	—	—	—	—	41.7	41.7	12
	Total tar	24.2	34.3	58.6	0.8	—	—	—	—	40.6	41.4	128
	Pitch and tar	54.2	27	81.2	0.5	0.1	0.6	—	0.8	16.8	18.8	1 001
Tar-distilling	41.6	26.5	68.1	1.5	0.3	0.6	—	4.0	25.3	31.7	331	
Gasworks	38.9	15	54	—	1.8	2.6	—	1.8	39.8	46	113	
Coke-ovens	50	25.9	76	0.7	0.2	0.9	—	1.6	20.6	24	1 445	
Total pitch and tar	33.3	48.2	81.5	—	—	3.7	—	8.4	46.6	75	27	
Creosote oil	Creosote-storage and proofing of timber	—	25	25	—	—	—	—	—	—	—	12
	Bricks and pottery	23	41	64.1	—	—	2.5	—	2.5	30.8	35.9	39
	Total creosote	60	40	100	—	—	—	—	—	—	—	5
Anthracene	Purification of anthracene	53.7	22	75.7	0.8	0.2	0.7	—	1.2	21.3	24.3	2,353
	Total pitch, tar and tarry products	11.8	17	28.8	6.8	1.2	0.7	0.27	1.6	60.4	71.1	1 419
Shale oil and mineral oil	Cotton	54.3	63.1	7.0	—	—	—	—	—	29.8	36.9	57
	Refining of shale and mineral oil	8.8	45	2.5	—	—	—	—	—	57.5	55	40
	Metal working	22.5	50	—	—	—	16.6	—	7.7	33.3	50	6
	Wool and worsted	50	—	—	—	—	—	—	—	61.5	69.2	13
	Other	23	7.7	30.7	—	—	—	—	—	—	—	—
	Total shale oil and mineral oil	12.2	18.4	30.6	6.6	1.1	0.7	0.3	1.5	59	69.3	1,535

N.B. 23 of the 3921 sites were not included in view of possible contact with both oil and tar and its products.

had been in contact first with mineral oil as cotton-mulespinners and then with tar as gasworkers (5), cable-layer (1), or oil-gas maker (1), or with creosote in the making of firelighters (1), or in substantial contact with both types of agent at the same time, as in the case of a rope-machinist in contact with wood-tar, who also lubricated his machine.

1 NATURE OF THE DISEASE

The disease begins as a papilloma of keratotic new growth which, in a few cases, may fall off without treatment (Fig. 1), or the worker (Fig. 16) may even adopt the undesirable procedure of paring it with a knife or scraping it with some abrasive, such as the striking-side of a matchbox, without apparently accelerating the onset of malignancy. Otherwise it may remain dormant for months or years (17 years in the case of one creosoter of wood, see Fig. 15) before assuming malignancy in the form of an epithelioma, either squamous-celled or basal-celled (rodent ulcer, Fig. 3). Of the latter there were at least 93 (or 2.4%) in this series. 72 were in workers in mineral oil² (Fig. 3), and 68 of these were in cottonworkers (making a percentage of 4.7 of the cutaneous epitheliomata in that trade, including a mixed basal-celled and squamous-celled carcinoma on the site of a birthmark on the right cheek of a cotton-mulespinner). The remaining 21 rodent ulcers were in workers in pitch, tar, or tarry products (Fig. 4).

In some cases the growth may occur on only one cutaneous site at one particular time, while in others more than one growth may appear at the same time on the same or different cutaneous sites (Fig. 11). One or more of these may assume malignancy, and, in one anthracene-maker in this series who contracted multiple growths of both forearms after 29 years of work, all were malignant.

Although the growth may be successfully removed by the surgeon or the radiotherapist, there is no guarantee that a similar growth may not arise later on another part of the skin of the same or a separate site, after a short or long interval. Subsequent primary growths may arise throughout the lives of men successfully treated for earlier growths. At least 326 men in this series had as many as 2-14 new growths within 3 months to 28 years, though all had not necessarily reached the malignant stage before they were treated.

If treatment is refused by the patient, or is unsuccessful for a primary epithelioma, death from metastases will eventually occur in approximately 2-3 years in the case of a squamous-celled carcinoma, but in the case of a basal-celled carcinoma (rodent ulcer) the fatal issue may be deferred for 7-20 years, as exemplified in the present series. If treatment is successful, the patient may live for many years until he dies of some other disease to which the general population is liable, or he may die of a subsequent primary cancer of an internal site such as larynx, lung, oesophagus, colon, rectum, liver, bladder or prostate, of which there are examples in this series.

2. SITE OF ELECTION

Although the new growth may affect any of the cutaneous sites the head and neck and upper limb (representing exposed

parts) and the scrotum (representing a covered part) are mainly affected. The lower limb (including the groin) appears to be affected in pitch- and tar-workers in only 1% of the cases, whereas in oil-workers (Fig. 18, 19) it is affected nearly eight times as often (7.7%), the trunk in under 1% both in pitch- (Fig. 17) and tar- (Fig. 16) workers, and in mineral-oil workers; while the penis is affected in only 1 to 1.5% in either type of worker. In the few cases of women, of whom all were in textile trades³, the disease was mainly on the exposed parts, the upper limb being the main contributor, though the external genitals were affected in 4 cases.

The selection of the site appears to depend mainly on two factors, the nature of the occupation, such as applying the chemical to a particular site, and the physical properties of the chemical. Dust of pitch, or the fume from hot tar, may permeate the atmosphere, alighting on exposed parts or even finding its way between clothing and skin, or mineral oil may drip, soak, and penetrate through clothing. In certain cases, individual habits have to be considered—such as lefthandedness, or application of the fingers or a cloth permeated with the chemical to a particular site, including even the possibility of use of oily waste on exposed parts and even, when in the lavatory, on the ano-perineal area and, in the case of females, the external genitals.

It will be seen from Tables I, II and III that in those workers in whom the exposed parts are especially affected, the head and neck is the principal contributor in makers of patent fuel (Fig. 5), electrical equipment (Fig. 8), workers in tar distilleries (Fig. 10) and gasworks (Fig. 6) and possibly in the small numbers of cotton-twinner-doublers, cotton-weavers (Fig. 2) and woollen workers, the upper limb in cable-makers, proofers of fabric, creosote-oil proofers and storers (Fig. 15), shale-oil refiners (Fig. 12) and female textile-workers, while both these exposed sites contribute substantially in those making optical lenses (Fig. 7), roads and road material, nets, or oil-gas. The scrotum and head seem to be more or less equally affected in coke-oven workers.

The covered parts are represented in the vast majority of cases by the scrotum, which is especially affected by pitch in loading at wharves, by the fume of tar in those engaged in the manufacture of producer-gas and in coal-carbonization, by creosote oil in the manufacture of bricks, or by mineral oil in cottonworkers, such as those employed in cotton-carding and preparatory processes, and especially in cotton-mulespinning (Fig. 20).

The question of the rarity of the disease on the palm of the hand or its absence from the sole of the foot (as, for instance, in cotton-mulespinners who walk about with bare feet on an oil-soaked floor) is possibly to some extent explained by the special texture of the skin or, in the case of the palm, the greater chance of removal of the chemical by chance handling or premeditated drying than in the case of the dorsum of the hand. There is, however, a case of epithelioma on the palm of the hand of a card-room operative (Fig. 13) and on the dorsum of the foot of a cotton-mulespinner (Fig. 19), while a record exists of a sarcoma on the sole of a cotton-mulespinner's foot, which had been injured by a penetrating nail.

² Dr. Alexander Scott, of Broxburn, informed me that he had come across only six cases of rodent ulcer during his periodic medical examination of shale oil workers in many years.

³ In 1946 however 2 cases have occurred in women aged 37 and 47, employed, because of the war, for 4½ and 4 years respectively as labourers at tar distilleries, the epithelioma being on the right cheek of the former and on the neck (Fig. 9) of the latter.

ILLUSTRATIONS OF CHEMICALLY - INDUCED OCCUPATIONAL CANCER OF THE SKIN

(FIG 1—20)

S A Henry

FIG 1 From the late Dr W D Jenkins



FIG 1 Sessile wart on the left cheek of a man aged 42 employed as a pitch-worker at a tar distillery. It made no progress and finally necrosed 4 weeks after the photograph was taken

FIG 2 From the London Hospital

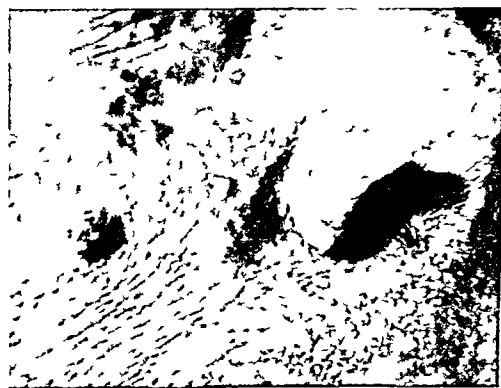


FIG 2 Epithelioma on the right cheek of a man aged 45 employed for 31 years as a machine-minder in weaving shed and other departments of a cotton mill

FIG 3 From Dr Alexander Scott Broxburn



FIG 3 Rodent ulcer below the right eye of a man aged 63 employed for 20 years in the paraffin sheds of a shale oil refinery

FIG 4 From the Ernestine Henry Collection



FIG 4 Rodent ulcer on the face of a male aged 54 years employed as a ploughman for 9 years sugar refiner for 1 year and anthracene worker in the manufacture of synthetic dyes for 25½ years. Note pigmentation of areas of skin normally exposed

FIG 5 From Dr C C R Down n Cardiff



FIG 5 Epithelioma on the nose of a man aged 47 employed for 14 years as a patent fuel worker. This was a fourth primary growth the first papilloma having appeared on the right lower eyelid 5 years before followed by growths on upper lip and left eyelid. He has since had 12 subsequent primary growths within 9 years on neck and face including upper and lower lips cheek forehead and nose

FIG 7 From the Royal Cancer Hospital (Free)



FIG 6 Epithelioma on the chin of a male aged 50 employed as pumpman in a gasworks for 24 years

FIG 7 Epithelioma on the chin of a male aged 38 employed as a blocker in the manufacture of optical lenses for 18 years

FIG 8 From the Royal Cancer Hospital (Free)



FIG 9 From the Royal Cancer Hospital (Free)

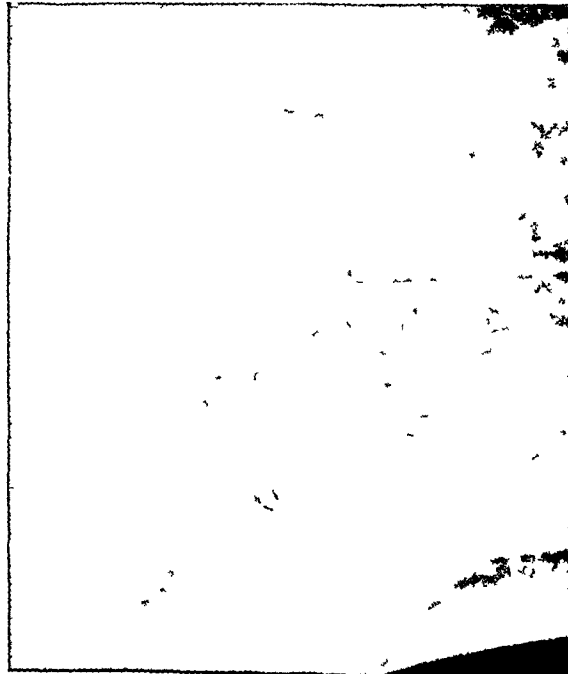


FIG 8 Epithelioma on the scalp of a man aged 53 employed in the manufacture of carbon brushes for electrical equipment for 26 years, and then with no direct contact with pitch for 1 to 2 years

FIG 9 Epitheliomata on the neck of a female aged 47 employed as a labourer at a tar distillery for 4 years

FIG 10 From the late Dr W. D. Jenkins



FIG 10 Epithelioma on the right side of the neck below the ear of a man aged 45 employed as a tar stillman in contact with tar, creosote and naphtha for 29 years. This was a third primary growth, the preceding ones being on nose and ear

FIG 11 Multiple epitheliomata (neck and left arm) in a man aged 76 employed as a cotton mulespinner for 55 years and then as oiler in a cotton mill for 12 years



FIG 12 Epithelioma on the left wrist of a man aged 56 employed as a paraffin worker at a shale-oil refinery for 13 years

FIG 11 From the Ernestine Henry Collection

FIG 12 Dr. Alfred L. S. t. Broxburn



FIG 13 From the Ernestine Henry Collection



FIG 13 Epithelioma on the palm of the left hand of a man aged 53 employed as a stripper and grinder in the card room of a cotton mill for 35 years

FIG 14 From the Ernestine Henry Collection

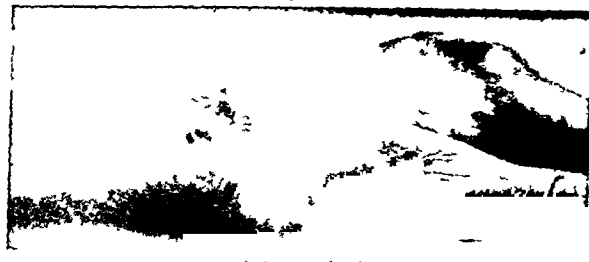


FIG 14 Cancer on the hand in a male aged 31 years employed as a cotton mulespinner for 7 years and after 5 years interval in the army as a gas retort stoker for 7½ years

FIG 15 From the Ernestine Henry Collection



FIG 15 Epithelioma on the dorsum of the right hand of a man aged 66 employed in loading and creosoting railway sleepers to the age of 57 and then as a store keeper. The growth commenced as a wart 17 years before, at the age of 49

FIG 16 From the Ernestine Henry Collection

PLATE 4 (FIG 16—20)

FIG 17 Dr C C R Downing Cardiff

FIG 16 Multiple benign keratotic new growths on the skin of a man aged 75 employed as a carter at a tar distillery for 50 years, formerly as a coal carter, he stated that he reduced many of the growths with the abrasive edge of a matchbox

FIG 17 Neoplasms on skin of chest wall of a man aged 22 employed as a patent-fuel worker for 2 years

FIG 18 From the Ernestine Henry Collection



FIG 18 Epithelioma on the left leg of a man aged 47 employed as a cotton-mulespinner for 37 years. He had an epithelioma of left arm at the same time

From the Ernestine Henry Collection

FIG 20 From the Ernestine Henry Collection

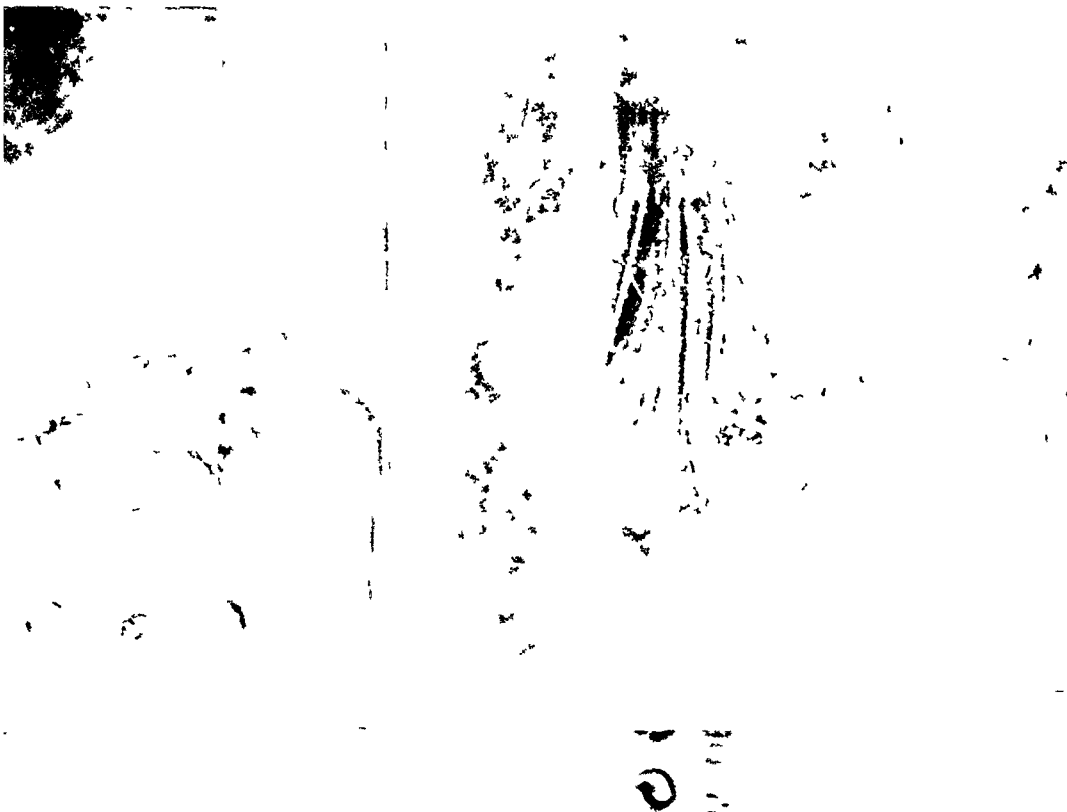


FIG 19 Epithelioma on the right foot of a male aged 55 employed as a cotton-mulespinner for 45 years. He worked with bare feet

FIG 20 Epithelioma on the left side of the scrotum of a man aged 46 employed as a cotton mulespinner for 36 years

TABLE III
ANALYSIS OF 1,389 CASES OF CUTANEOUS EPITHELIOMATA IN WORKERS IN THE COTTON TRADE
ACCORDING TO THEIR OCCUPATION

The letter R with attached numeral denotes the number of rodent ulcers included in the larger number (the incidence of rodent ulcer being 4.7% of the total number of cases)

OCCUPATION	NUMBER OF CASES	NUMBER OF PERSONS	NUMBER OF SITES	SITES								
				Head and neck	Upper limb	Lower limb	Trunk	Groin	Peri	Clitoris	Scrotum	Vulva
COTTON												
Drawing	3	3	3	—	—	—	—	—	—	—	3	—
Carding, males (ex-mulespinner)	12	12	15	2	2	1	—	—	—	—	10	—
" " (ex-mulespinner)	8	8	8	1R	4	—	1	—	—	—	2	—
" " females	2	2	2	2	—	—	—	—	—	—	—	—
" " females	7	7	7	1	5	—	—	—	—	—	—	1
Roving, males (ex-mulespinner)	3	3	4	2R*	—	—	—	—	—	—	2	—
" " females	7	6	7	—	—	—	—	—	—	—	7	—
" " females	6	6	6	2	3	—	—	—	—	—	—	1
Mulespinner, males females	1 295	1 237	1 319	143R**	213R*	94R*	8R*	16	21	—	819R*	—
" " females	1	1	1	—	—	1	—	—	—	—	—	—
Doubling (twinner)	4	4	4	1R	3	—	—	—	—	—	—	—
" " (ex-mulespinner)	1	1	1	—	—	—	—	—	—	—	1	—
" " (male)	2	2	2	—	—	—	—	—	—	—	2	—
Winding, females	2	2	2	—	1	—	—	—	—	1	—	—
Weaving, males (ex-mulespinner)	11	11	11	6R*	2	—	—	1	1	—	1	—
" " female	2	2	2	—	1	—	—	—	—	—	1	—
" " female	1	1	1	—	—	—	—	—	—	—	—	1
Labouring (ex-mulespinner)	2	2	2	—	1	—	—	—	—	—	1	—
" " (ex-mulespinner)	5	5	5	—	1	1	—	1	—	—	2	—
Maintenance (ex-mulespinner)	6	6	8	2R*	2	—	1	—	1	—	2	—
" " (ex-mulespinner)	5	5	5	1	2	—	—	—	—	—	2	—
Printing and dyeing (calico)	2	2	2	—	1	—	—	—	—	—	1	—
COTTON WASTE												
Breaking up	1	1	1	—	1	—	—	—	—	—	1	—
Washing sponge-cloth (ex-mulespinner)	1	1	1	—	—	—	—	—	—	—	—	—
Males, total	1,372	1,313	1 402	165R**	233R*	96R*	10R*	18	23	—	857R*	—
" " percentage	—	—	100	11.7	16.5	6.8	0.7	1.2	1.6	—	61.1	—
Females, total	17	17	17	3	9	1	—	—	—	—	—	3
" " percentage	—	—	100	17.6	52.9	5.8	—	—	—	—	23.4	—
Total males and females	1,389	1,330	1 419	168R**	242R*	97R*	10R*	18	23	1	857R*	3

3 CAUSAL AGENTS IN RELATION TO OCCUPATION

The main trades or occupations which contribute and, as far as possible the causal agents concerned, are shown in Table I, but in certain occupations a worker may encounter more than one carcinogenic agent and, further, he may occasionally change from one occupation in which there is contact with one type of agent such as tar, to another occupation in which there is another type of agent such as mineral oil or vice versa (see Fig. 14)

It must be emphasized that there are many persons who do not yet appreciate the legal requirement of notification of industrial disease or the relationship of a particular occupation to one or more recognized carcinogenic agents

For instance, before 1923 it was not realized by anyone except perhaps the late Dr S. R. Wilson, of Manchester, that the disease in cottonworkers was due to mineral oil but increasing knowledge from that date is reflected in the rise (Graph 1) in the number of notified cases. The numbers from this source reached their maximum of 101 in 1927 and 1928, since when there has been a gradual decline in the number of cotton-workers notified

The general fall from 1940 is due no doubt to various war conditions but the sharp rise since 1942 is due to a large

extent to the inclusion in the absence of a pathological examination, of an increasing number of cases of keratotic new growths, a substantial number of which are probably as yet benign. These are notified when they come to light at the periodic medical examination of certain pitch- and tar-workers, so wisely instituted by certain firms in order that early treatment usually at a radiological centre may be forthcoming—usually without loss of working time. Further the same men may be notified several times in one year for growths occurring one after the other on separate sites

Pitch, Tar, and Tarry Products

Apparently the term "tar" originally referred to the viscous residue remaining after the destructive distillation, at a high temperature, of wood, especially pine. Later it was applied to the product similar in appearance produced by the destructive distillation of coal, mineral oil, vegetable oil or even skin. If it is further heated there remains a solid substance known as pitch, which is hard and brittle when cold, but pliable when hot.

During the process of distillation of coaltar, crude products can be separated out according to the temperature such as naphthalene, creosote oil and anthracene oil, which, after purification, provide individual solid compounds

Coal-pitch

Patent fuel. Briquette manufacture provided 610 cases in 364 persons employed in one or other capacity as beltman, blender, pugman, piler, screenman, slinger, stower, tipper, wheeler, weigher, and others on the plant, such as blacksmith, roadman, stoker, oiler and even ostler. One stoker employed for 9 years had previously been a stoker at a brickworks for 30 years, another man who had been a fuelworker for 31 years had transferred to a brattice-cloth factory, where coaltar was used, for 9 years, after which the epithelioma developed on his neck, and one man aged 34, who developed a growth on the right side of the cheek after 4 years as a pitchman, had previously spent his earlier working life at sea

GRAPH I. NUMBER OF CASES OF CUTANEOUS EPITHELIOMA NOTIFIED ANNUALLY FROM 1920 TO 1945

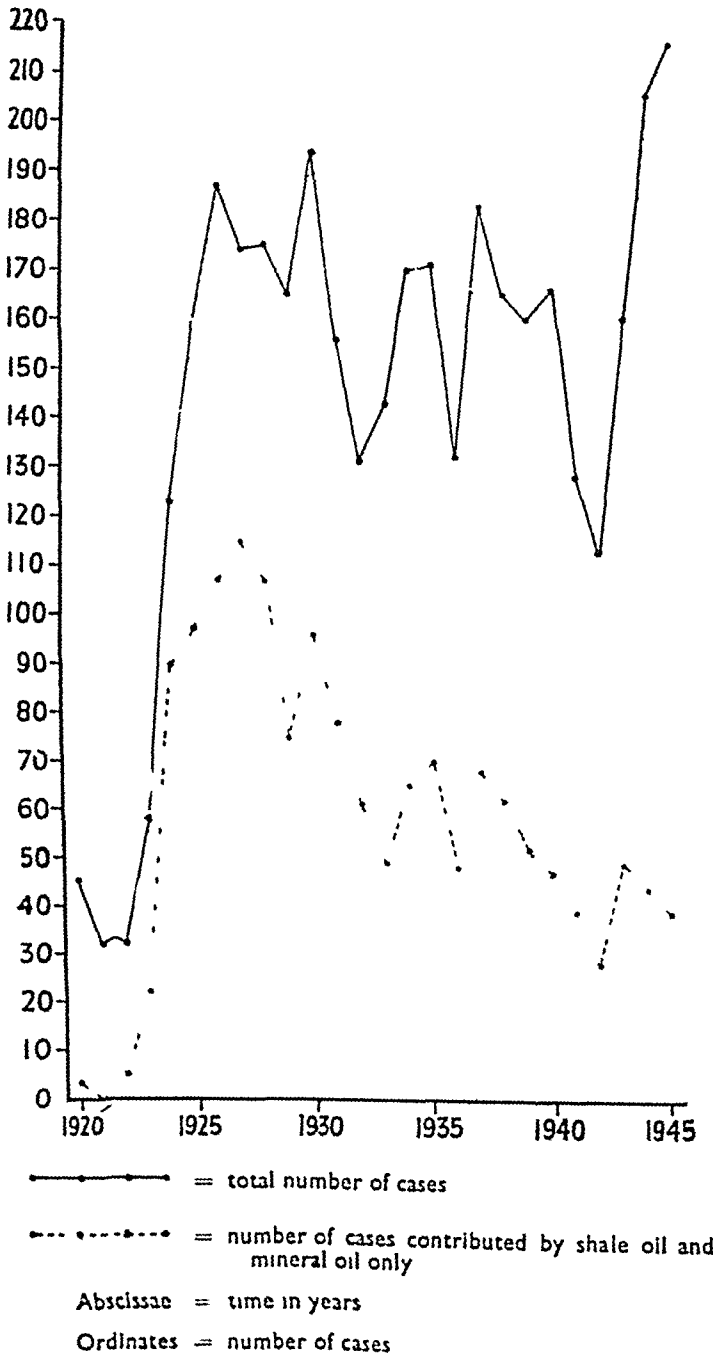
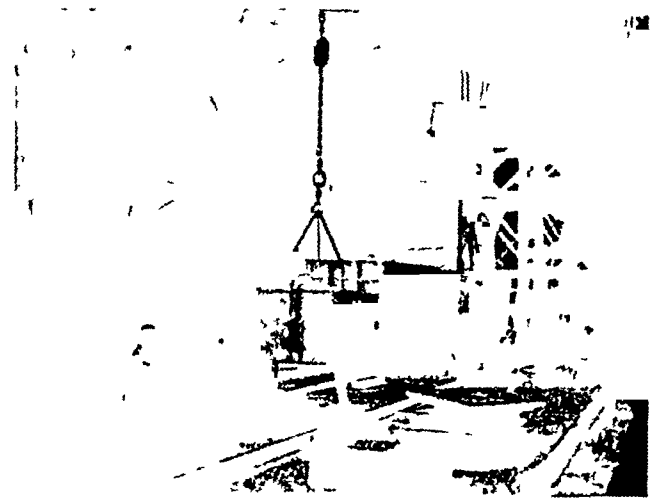


FIG. 21



By the courtesy of T. Roddam Dent & Son

Shipping pitch the bottom doors of the hopper wagon are opened, the pitch falls or is knocked through the bottom door to the hopper (covered by the truck). The tub, or skip, is at the bottom of the "pit", the "pit" door is opened by means of a lever, and the pitch runs from the hopper into the tub. When full, the tub, carrying 30-40 hundredweights [1,524-2,032 kg], is lifted and put on board and tipped into the hold of the ship

Pitch-loading at wharves provided 54 cases in 36 men employed at firms of wharfingers as stevedores, etc., loading pitch on to ships (Fig. 21)

Manufacture of electrical equipment, such as insulators, carbon electrodes and "electric brushes", was responsible for 29 cases in men who crushed, ground, mixed, moulded, pressed, weighed or loaded pitch, there was, however, also an important case of epithelioma of the forehead in one man who had been a clerk for 23 years only in the office adjacent to the factory in which the pitch-dust was generated

Manufacture of optical lenses was responsible for 16 cases in 11 persons⁴ using pitch for embedding the lens during the polishing process

Clay pigeons. There was an interesting case of a worker who for 3 years had been a melter of pitch with chalk for the manufacture of clay pigeons. A growth then appeared on the upper lip and another on the nose, and both proved, on histological examination, to be epitheliomata

Coal-pitch and Coaltar

Distilling of coaltar or coke-oven tar, which may be performed in a factory set apart for the purpose, or on a special plant in certain gasworks or coke-oven establishments, provided 939 cases in 538 males

It is not possible to divide the cases into those attributable to tar and those to pitch, for while the tar-stillman and the tar-pumper would be mainly in contact with tar, and the pitch-getter and -breaker in contact with pitch, the disease was found also among others employed in the works in such various occupations as fitter, drain-cleaner, platelayer, boiler-maker, boatman, bricklayer, scaffolder, acetylene-burner and boiler-stoker, one of whom described how he used pitch and creosote for firing. Even a time-clerk for 40 years and an ambulance-room attendant were not exempt, but the latter had previously been a fitter on the plant, while the history of removal of a keratotic growth from the head of a managing director is, no doubt, of interest

⁴ Seven similar workers were previously found to have keratotic growths on the head and neck, and on the upper limb, and in one case, after 1½ to 23 years of employment, on the scrotum, but as there was then no evidence that the malignant stage had been reached, these cases were not included in the figures

It must also be recorded that one man, with an epithelioma behind the ear after 35 years' employment as a coal-tipper on the plant, started working life as a patent-fuel worker, but only for the short period of 2 months

Coke-ovens There were 98 cases provided by 91 persons working at firms with coke-oven plants. At some such firms, which do not distil their coke-oven tar, workers are mainly in contact with such tar, but at others which also have a distillery plant, there would be contact also with pitch

Coaltar

Manufacture of coalgas There were 324 cases provided by 309 persons employed in the manufacture of coalgas. These included managers, retort-stokers, retort-setters and repairers, workers on mains and pipes, fitters, pipe-laggers, carpenters and other maintenance men, and yard-labourers

While coaltar is the main carcinogenic agent with which the gasworker comes into contact, there may be a limited contact in some cases with a lubricating mineral oil. For instance, an exhaust attendant stated that he used mineral and vegetable oils for engines and coalgas oil for the exhausters during the process of lubrication

In this connexion it must be pointed out that 4 of the men included in the figures had previously been in contact with mineral oil alone as cotton-mulespinners for 7 to 18 years, the epitheliomata appearing on the scrotum (2), hand (1), and lower lip (1) after 14 to 35 years' employment at the gasworks

Manufacture of electric cables was responsible for 23 cases in 22 men employed as tapers, compounders, coilers or maintenance men, or in handling tarred yarn, stacking cables, driving the machine for armouring the cables or making

FIG 22



From the Ernestine Henry Collection

Fixing or tarring of fishing nets showing the net after immersion

FIG 23



From Mr S H Wilkes

Topman on a producer-gas plant. Note position during prodding

asphalt troughs* to hold cables. One of the maintenance men who had been a crane-driver for 36 years had retired for 8 years before a growth appeared on the right ear, and the possibility of some contact with mineral oil in his case cannot be excluded.

Laying of electric cables This occupation provided 3 cases in men employed as cable-jointers but one who had been so employed for 18 years had previously been a cotton-mulespinner for 13 years

Road construction provided 22 cases, 13 were in 12 persons applying the material to the road and 9 in workers making the material known as 'asphalt' or tar macadam.

The 12 who were employed by public highways departments or by private road-contractors, included 7 in charge of the tar-boilers (one having retired for 5 years), 3 tar-sprayers, 1 "asphalter" and 1 pavior (and nightsoilsman)

Of the 9 makers of road-material who were employed at asphalt-works of private firms or on special plants at tar-distilleries, 8 were in contact with coaltar. The ninth was a worker at a lake-asphalt works for 23 years where I was informed that only *bitumen* (mainly natural from the Trinidad Lake, but occasionally artificial from a mineral oil) was used, but owing to wartime conditions he had become a civil-defence worker for 1½ years before the epithelioma appeared on the face. It may be recorded however, that

* The man in question used only a Trinidad Lake bitumen for the purpose, and in a previous communication I suggested that this case could be attributed to bitumen after 21 years' employment, but further enquiry has now shown that he spent only just over 2 years in the special asphalt trough department and that the previous 19 years were occupied in cable making, and so in contact with coaltar

FIG 24



From the Ernestine Henry Collection

Tarring of boats

one of the two tar-boilers had been a chimney-sweep in youth for 6 months, and the nightsoilsman had been a farm-labourer and started work in a cotton-weaving shed for one month 56 years before

Manufacture and repair of fishing nets (Fig 22) (e.g. work at ship-chandlers', netmaking, repair work at sea-coast towns) were responsible for 18 cases in 17 men, one man had an epithelioma of the left eyebrow, and in the following year a similar growth on the left hand. Some of these men were previously fishermen, as was the case with at least 9 of them, however, in 3 who had never been to sea, the growth appeared on the nose in two, employed for 8 and 12 years respectively, and on the scrotum of one employed for 61 years

Manufacture of producer-gas (Fig 23) provided 17 cases in 15 men continually employed for periods varying from 9 to 35 years at glass-bottle works, steelworks, synthetic-dye works, soapworks, shipbuilding works, shale-oil works or zinc-smelting works

It may be recorded, however, that in one of the scrotal cases, the man who was on the producer-gas plant at a shale-oil works for 16 years, had performed other employment previously at the same works for 14 years. This may have contributed totally or partially to the causation of the disease^{*}

Low-temperature coal-carbonization is a comparatively new method for production of a smokeless fuel and a coal-oil, in which a low temperature tar is formed. There were 11 cases in 7 men engaged on this process

In one interesting case, the man, who had been employed for 6 years as a retort man and had gone elsewhere for 2 years, was found to have a scrotal epithelioma when examined for re-employment in the carbonization process, thus showing the value of such form of medical supervision for a specific purpose

Proofing with coaltar of fabric, such as felt for roofing, and

^{*} Apart from these reported cases it may be of some interest to record that there was a similar case at the same oilworks, of a man who had been a labourer at the works for 9 years, then attended to the producer gas plant for 16 years, he then did odd jobs at the works for 3 years, after which an epithelioma developed on the scrotum. Another man, who had been on the producer gas plant of a steel works for over 21 years, developed an epithelioma on the skin of the pubis. At another works a man who had been on a producer gas plant from boyhood to the age of 32 developed a growth on the right side of the forehead which assumed malignancy 8 years later, resulting in death

brattice-cloth for preservation, for use in collieries, was responsible for 9 cases in 7 persons

Barge- and boat-repairing (Fig 24) was responsible for 3 cases in this series, but, in addition, there is an interesting record of an epithelioma on the forehead of a fitter at a firm of shipbuilders. This man was considered to have been in contact with the fume from tar-products in tank-barges under repair. There was another case of epithelioma of the penis of a boat-builder, so employed for 54 years, which ended fatally

Manufacture of earthenware pipes provided 3 cases in jointers of sanitary pipes or of stoneware conduits for electrical wire, using a tar composition, but in one of these so employed for 26 years there was probably previous contact with tar at a gasworks for 28 years

Manufacture and use of bitumastic paints Manufacture of such paint, from which a tar-content could not be excluded, provided an epithelioma on the face and on the scrotum of a man who for 16 years had been a boiler of a mixture of natural asphalt, mineral oil, bitumen, and coaltar, and the case of an epithelioma on the face of a painter who had been so employed for 30 years but for the last 3½ years had been continuously painting tanks with a bituminous paint

Repair of vehicles provided a scrotal case of a wheelwright at a corporation depot, who chipped tar off vehicles

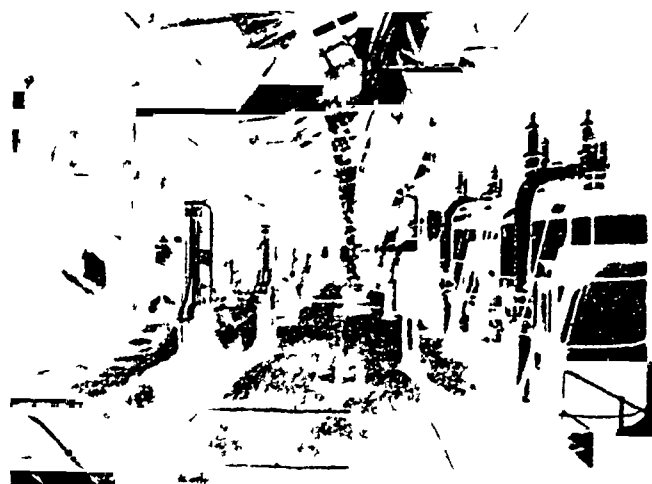
Haulage provided a similar case of a carter, mainly of pitch and tar, at a firm of carting contractors

Sailmaking at a shipwright company provided a case of epithelioma of the right ear, which, however, must be attributed to previous occupation at sea in contact with the sun's rays as well as tar, as no dressing of the sails with tar or any other proofing material was performed at this particular firm of shipwrights

Wood-tar

While wood-tar can be obtained sometimes from bobbin-makers in the north of England, who distil wood-shavings and scrap, the best examples are those from Russia (Archangel tar), Poland (Polish pine tar), and Sweden (Stockholm tar), and our medical colleagues in those countries should be able to give us valuable information on the extent of the carcinogenic properties of this substance

FIG 25



By the courtesy of the Gas Light & Coke Co

Manufacture of oil gas Carburetted water-gas plant containing the generators for making the water-gas and the carburetters and superheaters for evaporation and cracking of the mineral oil

Generally speaking wood tar is always used for coalsacks, as coaltar is too stiff, and the same applies to ropes. It may also, like anthracene oil, be used for making wagon-grease. But investigation has shown how often some coaltar seems to have crept into a process which at first seemed to be concerned only with wood-tar. For instance, in certain premises where nets are dipped mainly in wood-tar, a tank of coaltar may also be found when further enquiry is made. Hence in this series there is only one case⁷ of cutaneous epithelioma possibly to be attributable to wood tar. This was on the left hand of an attendant at a compound machine at a ropeworks (now defunct) where no coaltar was used but only Archangel tar, but even in this case it must be stated that the man also lubricated his machine with mineral oil.

Tar from Shale Oil and Mineral Oil

The term "oil gas" may refer to two different products one being the gas formed from the destructive distillation of shale oil (or more rarely other oils such as Russian mineral oil), and the other a carburetted water-gas in which mineral-oil spray at a high temperature is added during manufacture. Contact with the tarry residue of the oil at the retorts especially when these are being cleaned, cannot well be avoided, even in the latest apparatus, which may be considered as a closed one (Fig 25).

The manufacture of this gas from shale oil provided 7 cases, but in one of these, the man, who was a railway-carriage cleaner and shale-oil gasmaker for 38 years, had previously been a cotton-mulespinner for 10 years. The manufacture of carburetted water-gas from mineral oil produced 4 cases but in only one of these had the worker, so employed for 16 years not previously been in contact with coaltar.

Creosote Oil

Proofing of timber for railway-sleepers, pavement-blocks pit props, fences, etc., with creosote oil at creosoting works, railway works, sawmills, fencing companies and wood-pavement works etc., provided 14 cases, but there is also a record of a case of rodent ulcer on the face of a timber-creosoter at a tar distillery, and of an epithelioma of the scrotum of a creosoter of timber for fences at a firm of timber-merchants.

Creosote-oil storage provided 9 cases in 8 men loading and unloading creosote oil at works where this oil is specially stored.

Manufacture of bricks provided 10 cases⁸ attributable to the "brick oil" or "moulding oil" or "press oil", which is usually a creosote oil used to prevent the bricks adhering to the moulds. Nine of the men were, or had been, on the brick presses but the tenth was a machine-fitter, and although no doubt, he would come into contact with the creosote oil when maintaining the presses, contact with ordinary mineral lubricating oil could not be excluded.

Manufacture of furnace crucibles provided one case of scrotal cancer in a man who had been a pot-maker for 38 years at a steelworks. This was attributable to the creosote oil used during the process of making crucibles for melting the metal in the furnaces.

⁷ There is a record at another ropeworks where only Archangel tar was used of a fatal case (not notified) of scrotal epithelioma in a man who was on the tar pan but he was also a belt mender oiled machines and cleaned the sooty boiler flues. I have previously recorded 2 fatal cases of scrotal epithelioma, one in a man who manufactured the product and in another who brushed Stockholm tar on to coalsacks for 45 years these are more convincing.

⁸ A case of scrotal cancer in a brick burner for 15 years who had previously been a cotton mulespinner for 34 years was allocated to the list of cotton-mulespinners as attributable to mineral oil.

FIG 26



From Dr. Alexander Scott, Broxburn

Workers on the press expressing the oil from the paraffin wax at a shale-oil refinery

Manufacture of a disinfectant provided one case of epithelioma of the helix of the left ear in a man working at a chemical still. He had retired for 7 years after making a creosote disinfectant for 40 years though his previous occupation up to the age of 27 was not elicited.

Manufacture of firelighters. In connexion with the one maker of firelighters who had previously been a cotton-mulespinner and cotton-weaver, it may be of interest to state that there is also a record of a case not included in official figures of epithelioma of the left forearm of a man who had made firelighters (with peat blocks instead of wood for the body of the lighter) for 21 years. He had retired for 25 years but he too had previously been in the cotton trade as a cotton-weaver for 8 years and a farm-labourer for 6 years.

Records of other non-reportable cases attributable to creosote include that of a railway platelayer handling creosoted sleepers. After 31 years of this work an epithelioma developed on the left ear. An assistant chemist in the laboratory of a tar distillery had been testing creosote oils for 16 months when a keratotic growth as yet benign appeared on the right wrist.

Anthracene

Purification of anthracene or in one case loading boxes of it at a synthetic dyeworks for periods varying from 25 to 54 years was responsible for 5 cases on the upper limb or head including one of rodent ulcer (Fig 4).

Three others were engaged on the manufacture of anthracene at tar distilleries but only one of these (with multiple

FIG. 27



From the Ernestine Henry Collection

"Little piecer" (assistant to the spinner) in the cotton-mule-spinning room. Later he becomes a "big piecer" and subsequently a spinner.

epitheliomata of forearms) had been associated solely with the plant for 29 years, the other two having been workers in tar and pitch respectively.

Shale Oil, Mineral Oil and Bitumen

While shale oil is a mineral oil, it differs from the ordinary mineral oils which are obtained as such from under the earth's surface by sinking wells, in that it has to be extracted above ground from shale which has previously been mined. All these oils may be refined by distillation and fractionation, the final base or residue being either of a waxy (in the case of shale oil) or asphaltic (or bituminous) nature, or a mixture of both.

Among the products of the crude shale oil are *shale spirit* or *naphtha*, used as gasoline, motor spirit, solvent for india-rubber, fuel in special lamps, etc., *intermediate oil* for gas-making, gas-enriching, cleaning, oil-engine fuel, grease-making and fuel for the navy, *lubricating oil* for lubricating machinery, as in the cotton trade, etc., and *solid paraffin* (from which the oil has finally been expressed at the presses in the paraffin sheds of the refinery) used for making wax candles.

Bitumen is the term given to the product which appears in nature as Trinidad Lake bitumen or asphalt, or mixed with rock—as, for instance, Cuban Rock asphalt. It can, however, be extracted artificially at a temperature of approximately

350 to 400° C from a mineral oil, and is usually then called a "mineral-oil bitumen" in contradistinction to the natural product, though both are derived from mineral oil.

Shale-oil refining provided 52 cases in 42 persons, the majority of whom were employed in the so-called paraffin sheds where the refined oil is finally extracted at the press from the waxy base (Fig 26), but others were in contact with the crude or semi-crude oil at the retorts.

Other oil refining Only 4 cases¹ have been reported from oil refineries in which shale oil is not refined, 3 being from mineral-oil distilleries or refineries, as pumpman, blender and grease-maker, and one from a linseed-oil refinery; but in the latter case the man in question was for 40 years a cooper of barrels, 75% of which had previously contained a mineral oil, and he had been retired for 7 years before the disease manifested itself on the scrotum, eventually causing death.

Cotton trade This trade provided as many as 1,389 cases in 1,330 persons. Of the 1,389 cases, 1,296 (or 93.5%) came from the mulespinning room (Fig 27), including 141 persons who had retired and 179 who, after many years as mule-spinners, had passed into other occupations still in the cotton trade (94), other textile trades (5), the metal trade (29), or into other lighter occupations (51). In addition, 48 ex-spinners were, somewhat arbitrarily perhaps, classified

FIG. 28



From the Ernestine Henry Collection

Strippers and grinders at a carding-engine in the card room of a cotton mill, showing dust cloud from brush before the days of stripping under exhaust ventilation.

¹ The case of a man with a keratotic growth on the hand after one year's work as a cleaner at a mineral-oil refinery where no cases of the disease occurred before or since was classified as more likely to be attributable to his previous occupation at a shale-oil refinery for 3 years.

under other causal occupations (29 in cotton and 19 elsewhere, as shown individually in Tables I and III) in view of the length of time therein and the shorter period in spinning. If these 48 be added to the other 1,296, the number of cases in persons who had at one period (however short) of their lives, been cotton mulespinners, would be increased to 1,344, thus showing that at least 1,296 (34.5%) or at most 1,344 (35.8%) of the total number of cases notified since 1920 were, or had been, cotton mulespinners, and that, of the 1,389 cases provided by the cotton trade 1,325 (or 95.3%) occurred in men who had spent some part of their working life as mulespinners (Fig. 27).

Of the 93 cases in 92 persons classified as other cotton workers 29 (including 7 females, 8 ex-spinners and 2 ex-ring-spinners) came from the card room (Fig. 28, 29), 16 (including 6 females and 7 ex-spinners) from the ring-spinning room, 14 (including 1 female and 2 ex-spinners) from the weaving shed (Fig. 30), 11 were mill maintenance men (such as engine tenters, mill engineers, oilers and greasers, etc., including 5 ex-spinners), 7 were from the doubling-room (twinner-doublers including 5 ex-spinners, and 2 ring-doublers), 7 were cotton mill labourers (such as bobbin-carriers, cop-packers, oil storemen and distributors including 5 ex-spinners), others were from the blowing room (3), winding room (2, both females), print and dye works (2), and the cotton waste trade (2, including a "deviller" who had been breaking up the waste for 63 years, and a washer of oily cloths for cotton mills at a spurge-cloth works for 29 years but even the latter had previously been a mule-spinner for 2 years).

Woollen trade The wool and worsted trades provided only 6 cases¹⁹ of epithelioma in 6 men employed as mule-spinner, carder, settler and wileyer, mill engineer or wool blender and machinery oiler, previously wool comber.

Other textile trades There was one case of cutaneous epithelioma in a man aged 49 who had been employed in a



From the Ernestine Henry Collection

Females at slubbing frames in a cotton mill

¹⁹ There are, however, records of 14 other cases of cutaneous cancer in wool workers: 6 on the penis (including 2 spinners), 4 on the scrotum (2 spinners and 2 fettlers) and 4 on the head and neck, including a rodent ulcer of the nose of a man aged 69 who had spent some 50 years in a woollen mill while a woollen and worsted weaver for 26 years who oiled looms once a week and spindles twice a day developed a cancer of the tongue.

FIG 30



From the Ernestine Henry Collection

Cotton weaver operating the loom

jute mill in contact with mineral oil for 27 years but went into the army for 6 years and was then in a coalgas department for 4 years before the epithelioma developed on the scrotum, and another in a camel-hair belting-weaver aged 42 who had been so employed for 23 years when the epithelioma developed on the scrotum, causing death in one year.

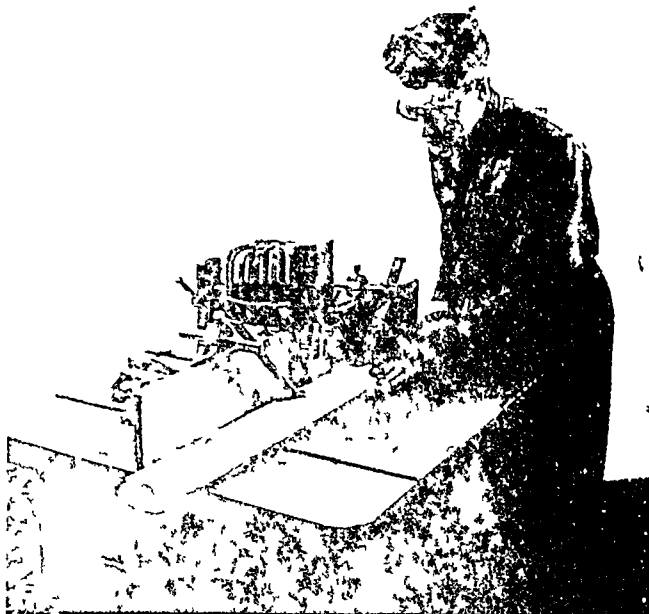
Metal working The working of metal may be divided into the production of the raw material in such places as iron-and-steel works, and its subsequent adaptation in engineering works.

In the case of one man who had been dipping pipes into coaltar at an iron works for 16 years when an epithelioma appeared on the calf and another on the right ear coaltar was no doubt responsible but in the other 49 (7 of whom had previously been cotton-mulespinners) the causal agent was apparently mineral oil 8 being associated with the production of the raw material as roller tube-drawer gun-smith nut and-bolt maker wire-worker oiler of axles at a blast furnace or engine tenter at an iron and steel works or arsenal, and 41 with engineering as driller, turner fitter cutter presser, polisher machine-setter fitter or engine tenter.

Repair of vehicles In addition to the wheelwright previously referred to, there was one case of epithelioma on the cheek of an engine tenter at a railway-carriage works and two cases of epithelioma of the scrotum of a fitter at a tram depot for 18 years and of a fitter at a bus depot for 19 years. The second of these had previously been a cotton-mulespinner for 8 years.

Rope-making Of the 3 cases occurring in rope-works, one was of a female machinist on a hackling machine for manilla hemp for 36 years. In this process as it is preparatory to any proofing, only contact with mineral oil could be elicited. Another case was of a male attendant at a compound machine at a rope-works (now defunct) for 30 to 35 years, where only Archangel tar was used but as he oiled his own machine the epithelioma which was on the left hand could not definitely be attributed to wood tar though the man in question would come mainly into contact with this substance. The third case was that of a maintenance man acting as firebeater and stationary- and locomotive-engine driver for

FIG 31



From the Ernestine Henry Collection

Woodworking machinery, showing a spindle-moulder being operated

39 years, when the epithelioma appeared on the left side of the scrotum, but he had been in previous contact with mineral oil as a cotton-mulespinner for 8 years

Woodworking (Fig 31) An epithelioma occurred on the scrotum of a fitter and crane-driver at a sawmill, of a wood-turner and spindle-moulder machinist at a cabinet-maker's for 37 years who also acted as engine oiler, and of a millwright at a factory making Venetian blinds

Coal-mining A colliery pumpman for 37 years had retired for 14 years when an epithelioma appeared on the scrotum. An engine-winding man at a colliery ironworks had been thus employed for many years when an epithelioma appeared on the face

Brewing A maintenance engineer at a brewery contracted an epithelioma of the penis after 42 years of employment. It may be borne in mind, however, that in addition to lubricating oil, such a man might well come into contact with a bituminous paint so frequently used in breweries

Match manufacture A storeman at a match factory contracted an epithelioma of the scrotum after 9 years in contact with mineral oil in the oil stores

Asphalt manufacture In only one case¹¹, in which the epithelioma appeared on the face of a firewatcher of the local Borough Council for 1½ years, could the growth be reasonably attributed to bitumen, as this man had been employed for the 22 previous years at an asphalt factory where it was definitely stated that only Trinidad Lake asphalt (or bitumen) was used

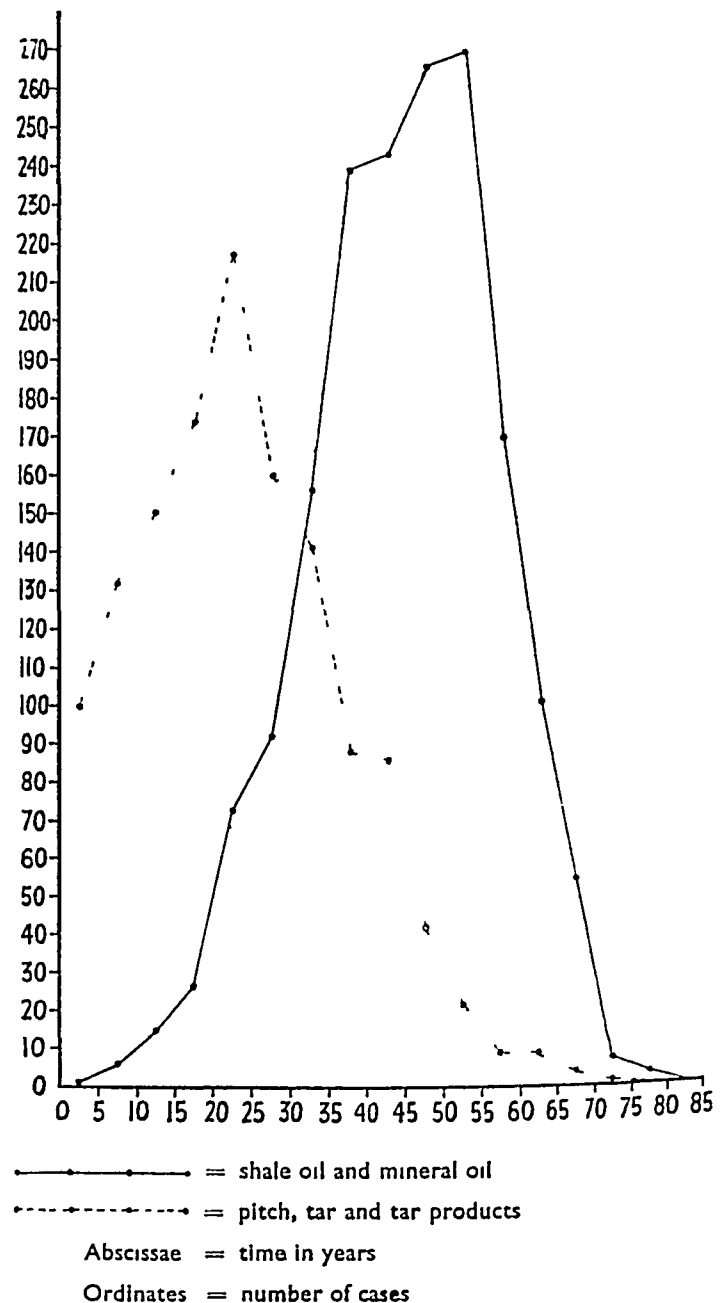
4 TIME ELAPSING FROM ONSET OF EMPLOYMENT TO MANIFESTATION OF THE NEOPLASM

In recent years, owing to a greater appreciation of the significance of so-called "pitch and tar warts", there has been an increasing tendency for firms, especially the larger

gasworks and tar-distilleries in which a periodic medical examination has been instituted, to notify cases on the first appearance of the growth. Treatment by radiotherapy is given without entailing loss of working time, and sometimes without a previous histological examination. Such cases are included in the statistics given in this paper unless there is definite reason for their exclusion. For example, a wart may have fallen off before the Examining Factory Surgeon sees the patient.

There is a difficulty in attempting to compare the time required from onset of employment to manifestation of the disease for workers in contact with pitch and tar and for

GRAPH 2 TIME ELAPSING FROM ONSET OF EMPLOYMENT TO MANIFESTATION OF A CUTANEOUS PAPILLOMA OR EPITHELIOMA IN 1,335 PERSONS IN CONTACT WITH PITCH, TAR, OR TAR-PRODUCTS COMPARED WITH 1,719 IN CONTACT WITH SHALE OIL, OR MINERAL OIL



¹¹ The two other cases in which there was contact with a bituminous paint have been included under the heading of "coal-tar", as there was no evidence that either of them had been in contact with bitumen alone, without the addition of coal-tar

those in contact with mineral oil, as the available data are not strictly comparable in both cases

I have previously illustrated in a graph the time required to produce actual malignancy on a particular site (the scrotum) in a particular class of operative (the cotton-mulespinner, in contact with mineral lubricating oil). In order to make the graph for pitch and tar comparable with that for mineral oil, I have now added cases on all cutaneous sites of all workers in mineral oil who are known to have been affected, and in addition I have included any known cases in which the growth might still have been in the precancerous or transitional stage. For instance, the mulespinner who had after 10 years' employment, a keratotic growth which did not assume malignancy for 6 further years, now appears in the graph 2 as 10 instead of 16

The shortest time elapsing from onset of work to manifestation of the growth in the 1,335 pitch- or tar-workers was 8 months in the case of a papilloma, 10 months for an epithelioma (pathologically confirmed) on the forearm of a pitch getter at a tar distillery¹², but previously employed above and below ground at a colliery for 38 years, and 1½ years for an epithelioma (pathologically confirmed) on the face of a mixer and grinder of pitch in optical lens manufacture

The shortest time for the onset of malignancy attributable to oil in 1,719 shale-oil or mineral-oil workers was 4 years in the case of a shale-oil worker with a growth on the dorsum of the hand, 8 years for a rodent ulcer on the face of an oil pumpman at a mineral oil refinery, and 9 years for a squamous-celled carcinoma on the scrotum of an oil-storeman at a match works. Further, it will be seen from the graph that onset of the maximum number of cases in pitch-

and tar-workers is 20 to 24 years after commencing work but as regards shale oil and mineral oil workers it is some 50 to 54 years. Hence it would appear that pitch (primarily) and tar are capable of producing the disease in man more quickly than mineral oil

The maximum time elapsing from onset of work to manifestation of an epithelioma in the case of workers in pitch tar or tarry products was 73 years. In this case, the man was a brick-presser who had been in contact with creosote for 48 years and who had retired for 25 years before the epithelioma appeared on the scrotum and penis. In mineral-oil workers, there was an epithelioma on the scrotum of a shale-oil worker after 40 years, and 75 years elapsed before the onset of epithelioma on the scrotum, neck and hand respectively of 3 cotton mulespinners, 2 of whom had commenced work from 1867 onwards when a lubricating oil containing shale oil had been on the market for about 4 or 5 years

* * *

ACKNOWLEDGMENTS—In conclusion, I should like to express my thanks to those firms providing photographs of certain processes, to Dr D W Smithers, of the Royal Cancer Hospital (Free), Fulham Road, London, for providing certain photographs of cases specially for this publication, and to all those, such as Dr C C R Downing, Examining Factory Surgeon for Cardiff, the late Dr W D Jenkins, Dr Donald Hunter and Dr W J O'Donovan, of the London Hospital, who have in the past presented photographs to the large collection (the *Ernestine Henry Collection*) of prints and photographs of industrial processes and diseases which is at present in my possession but which, in due course, will, I trust, find a permanent home in some suitable College, Institute or Centre

¹² Dr C. C. R. Downing, of Cardiff who performs a periodic medical examination of patent-fuel workers, has informed me that he has never come across a case of epithelioma in such workers in under 5 years

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THE ROLE OF ARSENIC IN CARCINOGENESIS

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Arsenic is a trivalent metalloid of atomic weight 75, and specific gravity 5.725. It is pentavalent in some of its compounds. It occurs in the free state but more often is found in compound form, e.g. realgar, which is arsenic disulphide (As_2S_2), orpiment (As_2S_3), smaltine, nickeline and mispickel. It is liberated from its ores by heating in enclosed metal retorts, when the element distils over and is condensed to a steel-grey mass of rhombohedral crystals which possess a metallic lustre. The metal in vapour form has a characteristic smell of garlic. There are three allotropic modifications—black, brown and yellow arsenic—and these are said to be non-toxic.

The most important commercial compound of arsenic is the trioxide, also known as white arsenic, arsenious anhydride and arsenious acid. It may occur naturally, but is usually made on a large scale by roasting arsenical pyrites, when it sublimes as a white powder. On oxidation it forms arsenic anhydride, from which some useful compounds—such as lead arsenate—may be obtained.

Apart from its being the starting-point in the manufacture of colours, such as Schweinfurth green (copper aceto arsenite) and Scheele's green (copper hydrogen arsenite), it is used in association with sulphur in the manufacture of sheep-dips.

Aromatic arsenicals are made principally for use in the treatment of venereal disease and some of the inorganic compounds have been used for many years for treating such skin affections as psoriasis and pemphigus.

Industrial Arsenical Risks

The worker in industry suffers an arsenical risk directly in the isolation of the element, in the manufacture of its compounds, in the processing of these compounds for industrial use, and indirectly by such side-effects as exposure to fume or dust during the isolation of other substances containing arsenic as a contaminant. Noteworthy examples as regards dust are to be found among the Schneeberg miners, and from fume by the accidental presence of arsenical impurity in acids used in the nitration of aromatic intermediates when arsine is evolved.

The risk of pulmonary cancer or other diseases of the lungs has been known for centuries in the Schneeberg area of the Erzgebirge, where cobalt occurring in the form of arsenide (smaltine) has been mined. Nowadays, the mining of bismuth has ousted cobalt, but nevertheless cases of pulmonary cancer still occur, and arsenic is still a factor among others to be reckoned with.

In 1879, Haerting & Hesse (1879), defining the malignant nature of the Schneeberg lung came to the conclusion that the inhalation of arsenical dust was the major cause of the

condition, but other writers, Osler, for example, maintained that cobalt was responsible for neoplastic change. Rostoki, Saupe & Schmorl more recently (1926) examined 143 miners in a random sample, 176 workers of the blue colour factory of Oberschlema, and 120 persons from the local population outside the mining and factory areas. Among the miners, 29 showed radiographically a clear pathological condition of the lungs, 17 pneumoconiosis, 4 tuberculosis, and 9 tumours. Rostoki *et al.* (1926) considered that the active irritant was arsenic and maintained that it was capable of producing tumours.

A typical analysis of Schneeberg mine dust gives

Silicic acid	50.00%
Alumina	14.65%
Ferrous oxide	7.50%
Calcium oxide	12.85%
Cobalt arsenide	0.19%
Nickel cobalt	0.08%

In the Schneeberg mines, as in Joachimsthal, radioactivity is pronounced, both the air and water of the mine being highly charged with radioactive particles, and the view is gaining ground that radium and its products, either alone or in conjunction with arsenic, can cause carcinoma of the lung. Some investigators would go so far as to deny arsenic any role in the etiology of this distressing malady, in which the course of the disease may be fatal in as short a period as 6 years from onset. Post-mortem, the lungs may show the presence of a simple carcinoma, perhaps an occasional lymphosarcoma, carcinoma of the pleura, of the bronchial glands and sometimes of the ribs, but only rarely. The period of contact with mine dust before onset of disease varies from 10 to 20 years, and there may be a lag period of several years after giving up mine work. The hewers are chiefly affected, although cases occur in mine masons and labourers. Hyperkeratoses of the palms of the hands occur in the men washing cobalt ores. These are suggestive of the condition of the palms following the internal administration of arsenic in the treatment of skin diseases.

In Britain, there is no record of the occurrence of lung cancer among the Cornish tin miners, who are definitely exposed to an arsenical risk, although J. Ayrton Paris, a physician practising in Penzance during the period 1813-1817, maintained that arsenical fumes from the smelting works occasionally caused scrotal cancer similar to that affecting chimney sweeps. Careful inquiry carried out later in this area disclosed no evidence in favour of Paris's claims. In any case the scrotum is a site very rarely attacked by arsenical cancer. Out of 75 cases reported in the literature only 4 were scrotal.

The first hint in Britain that arsenical dust might possibly damage the lungs was given by the late Sir Thomas Legge (1903), when he described a condition of irritation of the upper air-passages coincident with keratosis of the skin and pigmentation. These cases occurred in a factory in England engaged in the manufacture of sheep-dip from white arsenic and sulphur.

Pye-Smith (1913) collected 31 cases of arsenical cancer, among which were included 2 (skin) in sheep-dip workers. Merewether (1944) described a fatal case of pulmonary cancer in another worker, and recorded 3 similar cases notified in the previous 5 years.

I have records of a fatal case occurring in an English sheep-dip factory in a worker 55 years of age who had been

exposed to arsenical dust during a period of 43 years. Post-mortem examination of the right lung showed that the upper lobe had been replaced by a white neoplasm 2 in. by 2 in. [5 x 5 cm.] approximately, involving pleura and extending around subclavian vessels. The growth was necrotic and continuous with a large, ragged, ulcerated area in the base of the upper lobe, which contained recent blood-clot. This communicated with the main bronchus. The lower portion of right lung showed advanced bronchiectasis, and all bronchi were filled with recent blood-clot. The left lung was congested and emphysematous, and there was no growth in it.

On the skin a number of scattered, small slightly raised light brown, rounded areas approximately 3 mm diameter could be seen through the post mortem staining on the shoulders, upper chest walls, and upper arm. There was a slight scaling of the skin on the outer surfaces of both arms. There was no ulceration or perforation of the nasal septum.

The sections of lung and bronchial lymph glands revealed a columnar-celled adenocarcinoma in which there were less-differentiated areas and polygonal cell growth and some necrosis.

Three cases of cancer of the skin—one of which was complicated by the presence of pulmonary cancer—have been noted among British arsenical insecticide workers during the last 18 years and there can be little doubt that arsenic is a contributory factor among farmers gardeners and nurserymen who handle arsenical preparations extensively and who may use arsenic-contaminated materials such as soot and fertilizers.

The "Arsenic Theory" of Other Forms of Industrial Cancer

The common industrial cancers are (i) mulespinners' cancer, (ii) shale cancer, (iii) pitch and tar cancer, (iv) cancer of the urinary bladder.

The first type is prevalent in Lancashire among operatives engaged in oiling the mule-spindles with mineral oil. The origin of the earlier cases has been ascribed to the shale oil used which was well known to have a carcinogenic action on the workers who processed it in the shale-bearing belt of Scotland. The scrotum is commonly affected, and in Scotland chiefly the arms and legs. Pitch and tar cancer occur wherever pitch and tar are extensively and continuously handled and affect face and neck, chest back, arms legs and scrotum. Cancer of the urinary bladder is noticeably incident among workers handling such substances as benzidine, β -naphthylamine and aniline in the manufacture of intermediate dyes.

Is there something common to these various irritants that helps to bring about the same end-results? This question has been provocative of much thought, and several investigators, particularly Bayet & Slosse (1919) have become the champions of the arsenic theory.

These investigators found arsenic not only in the virgin coal, but also in the blood hair and urine of briquette workers using pitch. They claimed that pitch- and tar-cancer, and industrial cancers, generally were synonymous with arsenical cancer. This theory has been largely rejected by cancer investigators, among the reasons being

- 1 that some practically arsenic-free tars can cause cancer in mice

- ii coal hewers do not show a higher incidence than the general population
- iii the keratoses of palms and soles are not typical of pitch- or tar cancer, or mulespinners' cancer
- iv dibenzanthracene compounds of carcinogenic potency have been isolated from tar

So far as cancer of the urinary bladder is concerned, there might have been some support for their thesis 30 or 40 years ago, when this type of cancer was mainly associated with the manufacture of magenta. This is one of the earliest of the artificial dyes and was originally obtained by oxidizing with arsenic acid a mixture of aniline, *o*- and *p* toluidine. To avoid the arsenic risk nitrobenzene hydrochloric acid and iron filings have been introduced as the oxidizing material, the nitrobenzene acting as oxidant and the ferrous chloride as carrier.

Cases of cancer of the bladder, as already mentioned have been associated with the manufacture of benzidine and β naphthylamine. In this process aminations or reductions of nitro to amino groups may have to be made, using metal and acid as a reagent. The acid may contain arsenic as a contaminant. During the reaction it is changed to arsine gas, which is removed by local exhaust ventilation. It is thus obvious that arsenic can no longer be an etiological factor, since cases of bladder cancer still occur even with new techniques which practically eliminate the possibility of dispersion of arsenic in industrial processes.

Mulespinners' and shale oil workers' cancer are ultimately referable to the common contact of shale oil and it is interesting to record the views of Scott (1923) who has a wide experience of paraffin workers' cancer, on Bayet's theory. He says that

"it is also true that the dermatoses [shale oil] have some similarity to arsenic conditions, to some extent in the acute state, but showing more resemblance to arsenical conditions in the chronic types, but nevertheless it can be said that the paraffin workers' dermatoses are not due to arsenical poisoning. On analysis of an average sample of oil shale it has been found that arsenic is present to the extent of 0.00056% by weight and that in the blue oil which the workmen handle 0.000015%."

This blue oil is much purer than the Reichenstein water-supply later mentioned, where the concentration of arsenic is 100 times greater. In view of the infinitesimal concentration of arsenic in the oil the oligodynamic efficiency of this element would have to be of "atomic" potency to induce neoplasia and one has still to look elsewhere for the elusive cause of these industrial cancers.

Medicinal Arsenic Cancer

Signs of chronic arsenicism which may precede arsenical skin cancer are (i) hyperpigmentation or melanosis of the skin, (ii) keratoses.

Hyperpigmentation, usually of a brownish-yellow tint occurs in sites which are relatively more pigmented than the adjacent skin, e.g. in the axillae, areolae of the nipples, groin and perineum, and in pressure sites e.g. round the waist. Patches of reticular mottling are often to be seen. There may be other skin changes in the direction of chronic dermatitis and telangiectases.

The keratoses are the most noteworthy features associated with the intermediate process of cancerization. These commonly occur on the palms and soles and are regarded as precursors of cancer. The nodular form is characterized by numerous corn-like elevations about 3 mm in diameter

On the hands they frequently occupy the thenar eminence and the lateral borders and the back of the fingers, especially over the phalangeal joints. On the feet they occur on the heels and toes and may be confluent, giving the skin a leathery appearance.

These keratoses, which may be found on any part of the cutaneous surface, occur in about 80% of the collected cases of arsenical skin cancer. Sometimes they remain stationary or regress, and sometimes, after a long lag-period, physical change, such as fissuring with infection, takes place and the keratotic areas assume malignancy. Ulcers with hard pearly borders appear on the site of the fissures, and these gradually extend and invade the neighbouring tissues. They show little tendency to heal. These ulcers, almost invariably of squamous-celled type, are especially to be found on the fingers, palms, heels and toes. Histochemically, arsenic is demonstrable in the affected tissues.

Cancer has occurred in several cases in psoriatic patches treated medicinally during a long period with arsenic, and it has been assumed that the condition of psoriasis, although perhaps predisposing to the ultimate effect, did not play a causal role.

In the collected cases of arsenical skin cancer, over 50% have occurred in psoriatics, but a considerable number developed in subjects treated for acne, pruritis, pemphigus dermatitis herpetiformis, the various anaemias, bronchitis and asthma, where the intermediate preparative condition rendering the tissues liable to subsequent neoplasia-inducing insult was one of keratosis. The high incidence of cancer among psoriatics has led some investigators to the conclusion that psoriatics are predisposed to skin cancer, quite apart from arsenic administered in their treatment. Arsenical epithelioma may occur in skin which has not undergone a keratotic preparation.

Jonathan Hutchinson (1887) described 5 cases of skin cancer supervening after arsenic medication for psoriasis over a long period. In all cases a local keratosis had preceded the cancer. Earlier cases had been described by other investigators, but these authors did not associate arsenic medication with the ultimate neoplastic condition. It is held that trivalent arsenic is incriminable in the development of malignant change, and that the pentavalent variety has little or no effect in stimulating cell-proliferation. The cacodylates, which are pentavalent, have been frequently used as medicaments, but there is no evidence to show that they have exercised a carcinogenic action.

In the collected cases of arsenical skin cancer developing after medicinal treatment with arsenic, it has been noted among over 140 cases, that exposure to arsenic during treatment varied from 6 weeks to more than 30 years, and in the great majority of cases cancer resulted only after the drug had been administered for a very long period—up to 30 years—although there have been some instances where the exposure was of short duration. The average total quantity administered to each patient was of the order of 430 grains [28.7 g].

Bowen, in 1912, described a skin affection with a typical epithelial proliferation as a new type of precancerous dermatosis. It was marked clinically by multiple, slightly elevated papules of dull-red colour, covered with scaly crusts and arranged in groups. Histological examination disclosed a neoplastic process with abnormal keratinization and amitotic cell-division producing giant cells. The neoplastic process may remain intradermal, but in about 20% of the

cases an infiltrating and metastasizing squamous cell epithelioma develops. Many investigators alleged that Bowen's disease was due to arsenic, but Montgomery (1939) stated that in his 5 cases of Bowen's disease, arsenic was not administered nor were keratoses nor pigmentation present.

Kennaway (1925) reviewed the distribution in 38 cases published up to that time. These were mostly of medicinal origin. He confirmed a well-known tendency of arsenic to affect the fingers and toes in contrast with cancer in tar, pitch and shale-oil workers, in whom the parts particularly affected are the scrotum, head and neck. Among 75 arsenic growths in 38 patients, 46% were located on fingers, legs, feet, toes and trunk, 23% on arms and hands, 23% on scrotum, penis, head, face, neck, eye and eyelid, 8% in other parts. Kennaway criticized the assertion of Bayet & Slosse (1919) that the scrotum and its neighbourhood are the favourite sites for arsenic cancer.

Non-industrial Arsenical Intoxication

Cases of arsenical intoxication, in some instances developing cancer, have been described as occurring in Reichenstein (Silesia) and Cordoba in Argentina, owing to the relatively high concentration of arsenic in the public water-supply. In Reichenstein, 1.22 mg % of arsenic was found in one water sample. In Cordoba some of the drinking wells contained 0.45 mg % arsenic. Some 65 cases of skin cancer have been reported in the latter area, and these presented all the major characteristics of medicinal arsenical cancer.

The Reichenstein cases are not so well authenticated but it is interesting to note that, in addition to the classical signs, perforation of the nasal septum was often observed. Reichenstein cancer has largely been conquered by the supersession of crude smelting methods by modern techniques, so that the town, with its new water-supply and freedom from airborne arsenical dust, can now boast that its public water contains only 0.0015 mg % of arsenic.

Experimental Findings

Many experiments have been carried out on various animals during the last 25 years in an attempt to shed some light on the mechanism of arsenical carcinogenesis.

Leitch & Kennaway (1922) skin-painted a batch of 100 mice with a 1.8% alcoholic solution of potassium arsenite. This preparation, which was later reduced in concentration to 0.12%, was applied 3 times daily. After 86 days, a tiny wart appeared at the site of application among one of the few survivors. A second wart developed a fortnight later, and histological examination showed it to be a squamous-celled epithelioma.

In a second attempt, Leitch (1923) could not elicit any carcinomatous response in his animals. It is possible that the chief factor militating against the success of these experiments is the high toxicity of the arsenic salt, which does not permit the animal to live long enough for its tissues to be precancerized.

Other investigators, e.g. Lipschütz (1924) and Raposo (1928), produced hyperkeratosis and hyperpigmentation, but no obvious malignant change.

Feeding animals with arsenic salts produced the same indeterminate results, although parenteral injections in mice, chickens and rabbits produced sarcomatous changes.

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OCCUPATIONAL CANCER OF THE BLADDER

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- 1 Causal agents
- 2 Industrial processes concerned
- 3 Acute bladder irritants not associated with carcinogenesis
- 4 Metabolism of bladder carcinogens
- 5 Occupational features of the disease
- 6 Legislation
- 7 Signs and symptoms
- 8 Pathogenesis
- 9 Pathology
- 10 Treatment
- 11 Surgical prognosis
- References

The correlation of occupation with incidence of disease often a matter of conviction in the minds of medical observers in daily contact with the affected persons may be very difficult to demonstrate by statistical or experimental methods. This is the more difficult if the disease in question is clinically not distinguishable from that occurring in the non-industrial population. The matter becomes easier if the occupation involved is associated with processes in which the affected persons have been exclusively engaged for a sufficient time. Clearly, if the numbers of workers in such processes are known and the incidence among them is recorded some certainty as to the occupational nature of the disease can be reached by suitable comparison with the incidence in the general population allowing for such factors for example as age and sex.

In the particular field of bladder tumours an attempt was made by Henry Kennaway & Kennaway (1931) to determine such correlation by examination and analysis of death certificates of cases of cancer and papilloma of the bladder in both sexes and of cancer of the prostate in England and Wales in 1921 and 1928. Calculations were made of the deaths that would be expected in a considerable number of different occupations, the populations of which were arranged in quinquennial age groups and these were compared with the actually registered deaths. Inevitably, difficulties were met with in establishing the populations at risk in sampling-errors, and in obtaining detailed information of clinical and occupational history.

Nevertheless, suggestive evidence was obtained that in occupations involving exposure to coalgas tar, pitch and soot there is a greater incidence of bladder cancer than in the general population. Having regard to the known presence of carcinogenic hydrocarbons in these materials, some such result might have been anticipated. Unfortunately Henry *et al* (1931) were unable to make a similar analysis for chemical workers as it was not possible to ascertain the populations at risk. It is in the chemical industry that the most striking evidence is obtained of a relation between bladder tumours and occupation. At various times it has been suspected that other agents might be responsible for bladder tumours in workers but those of which one can speak with some certainty as ultimate causes in industry are associated mainly with the manufacture of organic intermediates. It is of the disease as met with in this industry that this article will treat.

1 CAUSAL AGENTS

The condition has been named "aniline cancer", "dye-workers cancer" and "amino cancer". There are reasonable objections to all these names. Thus aniline is certainly not the only cause. Only a minority of dye-workers are exposed to the risk. "Amino cancer" is too broad a term since whilst the amino radical is probably essential there

ARSENIC AND CARCINOGENESIS

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Arsenic has also been combined with tar in a group of animal experiments with a view to studying its influence on the course of tar-cancer, but the results do not admit of a clear-cut interpretation, some experimenters indicating that it has a retarding action on tar-cancer growth, others the reverse. Carrel (1925) injected chickens with a mixture of embryonic chicken pulp and arsenious acid. Of 16 chickens 4 developed spindle-celled and sarcoma after a few days, and the tumours contained a virus-like filterable agent which may or may not have been produced by the arsenic.

As other investigators produced sarcoma after the injection of embryonic pulp alone the influence of arsenic is negatived, and it is possible that a virus contaminant had entered into Carrel's experimental animals.

Conclusion

It is difficult to assess the function of arsenic in the production of malignant change. It may act as a chronic protoplasmic irritant directly stimulating epithelial proliferation. On the other hand, because of its profound effect on cell oxidation, it may bring about an intracellular chemical breakdown liberating organic substances which are known to produce cancer experimentally. These substances may act at the site of their evolution or may be transported to distant parts to effect in time malignant change at their ultimate destination. The general development of skin melanin during treatment or exposure is suggestive, since melanins could very easily be the precursors of carcinogenic aromatic hydrocarbons.

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are enormous numbers of organic amino compounds which are certainly not involved in the causation of the disease. A considerable number of compounds employed in the synthesis of organic dyestuffs has been suspected as being, or giving rise to, carcinogenic agents, but hitherto only β -naphthylamine has been found experimentally to produce tumours localized exclusively in the bladder (Schar, 1930, Hueper, Wiley & Wolfe, 1938, Bonser, 1943).¹

The last-named worker used purified β -naphthylamine and has left no substantial doubt that this compound is a bladder carcinogen, although it is not as yet established whether it acts as such or as a precursor of the active carcinogen.

Aniline was held to be a bladder carcinogen by continental observers before it was apparent to British and American students of the disease. It is notable that in Britain and in the USA cases attributable to exposure in the manufacture of aniline are relatively very rare. This may be due to the conditions of manufacture, especially plant design. Aniline cases in our experience have arisen rather in the use of the base for other manufactures than in the production of the base itself. Experimental proof that aniline is carcinogenic is not extant.

Benzidine has not been shown to be a carcinogen in animal experiment, but clinically it is a potent cause of the disease (Berenblum & Bonser, 1937, Kennaway, 1924).

Much discussion has centred on the question of the possible carcinogenicity of α -naphthylamine, but the trend is to attribute such cases as have occurred among workers engaged in the manufacture of this base to the significant proportions of β -naphthylamine present in it as an unavoidable impurity. This arises from the fact that the nitration of naphthalene yields not only α -nitronaphthalene but also a small proportion (up to 5%) of the isomeric β -nitronaphthalene and hence, on reduction, a corresponding amount of β -naphthylamine. Experimentally, α -naphthylamine has not been shown to be a carcinogen. That other amino derivatives have been shown to produce bladder tumours in animals is well-known, e.g. 4'-amino-2,3'-azotoluene, 2,3'-azotoluene, but these tumours have been associated with additional tumours in other situations, whereas it is one of the remarkable characters of the disease as seen in industry that it is almost exclusively a disease of the bladder. Similar remarks apply to the recent interesting findings with 2-acetylaminofluorene which, fed by mouth to mice, led to benign and malignant tumours in the bladder, the liver and the uterus (Wilson, DeEds & Cox, 1941, Bielschowsky, 1944, Armstrong & Bonser, 1944).

The common factors in those compounds which, in industry, are responsible for the disease are

- i they are basic
- ii they are aromatic
- iii they are primary amines

The basic character is of great importance, for all the evidence points to the innocuous nature of the salts and the sulphonic acid derivatives. Whether this loss of carcinogenic activity is due to solubility, and presumably more ready excretion, or to some fundamental inhibition of the potent part of the molecule, or to some modification of metabolic changes which are essential to a transformation of the base to a carcinogenic molecule it is not possible at present to say.

Loss of basic properties is, of course, well known as greatly diminishing even the acute toxicity of aromatic amines e.g. the sulphonic acids of aniline do not produce methaemoglobin *in vivo* and the hydrochlorides of, say, chlor-toluidines, are quantitatively much less toxic than the bases.

Again, the integrity of the amino group appears to be necessary for the carcinogenic effect. Whereas some American investigators regard substituted naphthylamines with some suspicion, e.g. phenyl- α -naphthylamine and phenyl β -naphthylamine, no cases clearly attributable to these compounds have been reported. Large quantities of compounds of this kind are manufactured for the rubber industry, but cases among workers exposed to considerable dust of the final product over many years do not appear to come to light. Experimentally, neither of these compounds has shown carcinogenic properties (Shear, quoted by Hartwell).

The association of aniline with occupational bladder-tumours led some writers to throw suspicion on diphenylamine. In our experience, workers exposed to this compound appear to suffer neither acute nor chronic effects. Animal experiments confirm this. Nevertheless, Müller (1933), in his list of 59 cases, gives diphenylamine as the cause of the "fragliche Schädigung" leading to a bladder carcinoma. Alkyl derivatives of aniline (mono- and di-) have not, as far as we know, ever shown themselves to be carcinogenic even after years of exposure to them. On the other hand, acute symptoms of methaemoglobinaemia follow considerable exposure to these derivatives.

No suspicion that compounds other than aromatic are involved in the causation of cancer has ever arisen. Aliphatic primary amines are relatively much stronger bases, but no association with the disease has ever arisen either in the manufacture or use of these compounds. The complex polycyclic aromatic carcinogenic hydrocarbons do not show experimentally any tendency to select the bladder as the sole organ of attack, although it may be attacked in common with other organs.

The position of azo derivatives in the production of the disease is a matter of some doubt. This is, in part, due to the fact that workers engaged in the manufacture of azo compounds must come into contact with primary amines and it is therefore difficult to identify the responsible agent when a case of bladder tumour is detected.

Some recent work by Elson & Warren (1944) is suggestive in the particular case of azobenzene, which they found could be partly converted in rats to aniline and a water-soluble derivative readily convertible to benzidine by dilute acid.

The present position, then, as to the causation of these tumours in the dyestuffs industry, is that β -naphthylamine and benzidine are certainly causes, aniline and α -naphthylamine are possible, perhaps probable, causes. In our present state of knowledge, other compounds may be suspected, but clinical evidence and experimental support are not available.

2 INDUSTRIAL PROCESSES CONCERNED

Since the injury which later manifests itself as a bladder tumour occurs in the course of manufacture, it will be useful to refer briefly to the nature of the processes involved. It must, however, be pointed out that cases have occurred in dyers who have handled certain of the amines for the purpose of the preparation of an azo dyestuff for immediate use in the dye-bath.

¹ [See also article by G. M. Bonser (*BMJ* 1973) in this number.—Ed.]

² [See also article by F. Bielschowsky (*BMJ* 1974) in this number.—Ed.]

a. α -Naphthylamine

This is prepared by nitration of naphthalene, with the formation of α -nitro-naphthalene and a small proportion of β -nitro-naphthalene. Conversion to the amine is either by reduction with Fe and HCl or by hydrogenation with hydrogen under appropriate pressure. In either case a proportion of β -naphthylamine is present in the final product. By distillation, the amine is made available for the process of flaking, which yields a dry product readily giving rise to considerable dust. In modern plant considerable efforts are made to prevent

- i The evolution into the atmosphere of fume from the stills
- ii The emission of flake and dust from the flaking machine and from the containers (drums) into which the product is discharged

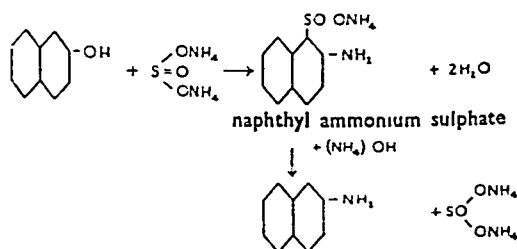
Formerly, before the hazard of this manufacture was fully appreciated the product was distilled and run off into open buckets which, after cooling in running water, were inverted. The solid truncated cone of amine was then broken into convenient lumps. In the course of years this led to a considerable number of cases of bladder tumour.

Thus, briefly, there are two distinct aspects of the process—(i) nitration and (ii) reduction and distillation.

In so far as it is possible to speak of "nitration men" and "reduction men", clinical observation and control indicate that the liability to bladder disease is confined to the latter such compounds as naphthalene and nitro-naphthalene being innocuous as far as bladder tumours are concerned. Whereas in former times the base was taken from the plant by hand to other points, for the production of such compounds as naphthionic acid, the more modern plants transfer the molten base through heated pipes to the sulphonators without the necessity for emergence of the base. There remains, however, a significant number of processes which require the separation of the base and, inevitably some degree of exposure of workers to the dust (mainly) of the product.

b. β -Naphthylamine

The manufacture of this compound is more complicated than that of α -naphthylamine. The starting material is β -naphthol, which is subjected to the action of ammonia and ammonium sulphite in an autoclave. The ammonium sulphite acts as a carrier of the NH_2 group thus



The separation and washing of the naphthylamine are followed by distillation and flaking.

The amination can also be effected in the vapour phase by passing β -naphthol and ammonia over alumina at high temperatures, but we are not aware that this process is used in Britain. The hazard of the process lies in evolution of fume and liberation of flake and dust. Except the amine (and possibly some di-naphthylamine), there is no compound appearing in this process which can be suspected of potential carcinogenic activity.

Many cases have occurred among workers in this process. Since all the evidence points to the base as at least part of the cause of the disease and since the main use of the compound is to prepare from it certain innocuous sulphonic acids, efforts have been made to prepare the naphthylamine sulphonic acids by starting from a sulphonated β -naphthol

and aminating at a later stage. Müller (1945) states that this has been done in Basel with good results. It has been stated that similar efforts have been made in Germany.

c. Aniline

The large-scale manufacture of aniline in Britain is carried out by first nitrating benzene and then reducing the nitrobenzene to the amine with Fe and HCl, the latter in quantities much smaller than seems to be required by any simple formulation of the reaction. The original report of cases of bladder tumours in dyestuffs workers (Rehn, 1895) described the latter as having worked in the manufacture of fuchsine, which involved the oxidation of a mixture of aniline, *ortho*- and *para* toluidine. But it is probable that these men were exposed to other aromatic compounds. Since that time cases attributed to aniline and its alkyl homologues have appeared in the Continental literature, but the rarity of even suspicious cases in USA and in Britain is possibly due to the manner in which the manufacturing operations are carried out and to the design of the plant.

It seems justifiable to say that the plant-design and plant-conditions (ventilation for example) are in general, such in British and USA aniline manufacture that cases of bladder tumour attributable to this compound are rare.

Nitrobenzene, always noticeable in the atmosphere of an aniline plant, is not carcinogenic.

d. Benzidine

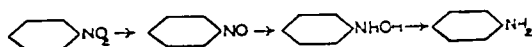
This compound is manufactured by various processes each of which has given rise in greater or less measure to cases of bladder tumour.

1. A method widely used is to react nitrobenzene, with or without organic solvents, with strong caustic soda solution and zinc dust, when, under careful control of temperature and avoidance of excess zinc, the nitrobenzene is reduced to hydrazobenzene with the intermediate formation of azoxybenzene and azobenzene. The hydrazo is separated and can now be converted to benzidine hydrochloride by the addition of ice and concentrated HCl. By suitable variation of conditions the mono- or di-hydrochloride can be produced, and passes into the aqueous layer. In addition to the benzidine hydrochloride, a significant amount of diphenylene hydrochloride (2,4'-diaminodiphenyl) is formed.

Benzidine base is formed by precipitating the sulphate and basifying with soda ash. The base is filtered off and can either be dried or, to obtain a pure benzidine, distilled in vacuo. Having regard to the recognized carcinogenic action of the base, the trend in manufacture is to reduce the quantity of base produced to a minimum, and to use the hydrochlorides in the subsequent manufacture of the dyes.

2. A second method is to reduce nitrobenzene electrolytically in the presence of alkali and a solvent for the hydrazobenzene thus formed.

The series of changes occurring in this reduction is somewhat complex and the particular end-product obtained depends upon the adjustment of conditions in which side-reactions take place between the products of the electrode processes. Thus, at the cathode, the electrochemical reduction, depending on the conditions, proceeds thus



each product depending for its appearance or its interaction with other products on the physical condition in which the reduction is occurring. The nitroso stage is, in any event, completed very quickly, as its good depolarizing properties promote its rapid reduction.

In suitable alkaline conditions, and with a properly chosen high over-voltage cathode, and with suitable solvents, the phenyl hydroxylamine is involved in side-reactions as well as reductions giving rise to azoxybenzene, azobenzene and hydrazobenzene, the two former being further reduced in the same conditions.

The transformation to benzidine is then carried out as in the zinc reduction process. The proportions of aniline and diphenylene formed are removed by salting out the benzidine, the former compounds being left in the mother liquor.

3 A third process, used mainly on the Continent, is to apply the reducing action of a sodium-amalgam-alcohol system to nitrobenzene, whereby hydrazobenzene and some proportion of diphenylene and azobenzene are produced.

The subsequent transformation to benzidine is as shortly described above.

As has been said each of these benzidine processes has in varying degrees led to the development of bladder disease in workers and, whereas the compound generally held to be responsible is benzidine (the base rather than the hydrochlorides), some consideration must be given to the possibility that the intermediate hydrazobenzene and the less-reduced form, azobenzene, may be involved.

Nitrobenzene and the other reagents do not come in question. Of the properties of diphenylene (2-4' diamino-diphenyl) we know nothing. Generally, it is held that hydrazobenzene is not carcinogenic, this view being based on statements that "reduction men" have not developed bladder disease. But this, even if accepted, is by no means equivalent to saying that the hydrazo-compound is innocuous. The fact is that, in the older plants, hydrazobenzene was readily in evidence whether (i) at the filters in the zinc process, or (ii) in the alkaline fine spray as well as at the filters, in the electrolytic process, and (iii) at the filters in the mercury method. That hydrazo spontaneously decomposes in the conditions in which it is likely to be found about a plant is certain.



Thus, those who know aniline to be carcinogenic and who know that azobenzene can, at any rate in the rat, give rise to aniline, cannot fail to regard hydrazobenzene as a potential menace. It has been stated by Auler (1937) that painting the skin of rats with hydrazobenzene elicited tumour development. This did not result, however, with mice or rabbits. This is a rather remarkable observation, if it can be confirmed, having regard to the complete failure by others to produce skin tumours with compounds known to be potent bladder carcinogens. Naturally, the degree of exposure of workers to the hydrazo compound was, even in the undesirable conditions of former years, not as intense as it was to benzidine itself and the conditions for its absorption were not so marked. For the former is present mainly in a wet form and is not dried or distilled, whereas benzidine was either dried or distilled and offered good conditions for absorption. The known great differences in susceptibility of men to the development of bladder tumours must make us pause before asserting that hydrazobenzene is innocuous in this respect. In our present state of knowledge, we take the view that the manufacture of benzidine should be regarded integrally as a hazard from start to finish and that the base

should be prepared only if the plant design is such as to preclude absolutely any maintained contact with, or exposure to, dust of the final product.

3 ACUTE BLADDER IRRITANTS NOT ASSOCIATED WITH CARCINOGENESIS

In the industries in which the carcinogenic aromatic amine bases are made or used, many other compounds appear which, whilst not as yet known to exert an influence on the bladder that may later manifest itself as tumour formation, certainly attack the bladder. Among these there are nitro compounds, amines, chloramines, nitro-amines, phenols, diamines, chlor-nitro compounds, and derivatives of amides. These compounds in general act acutely if a sufficient exposure and absorption have occurred. Signs and symptoms are overt, and appear to be completely removed with suitable treatment and removal from exposure for a time.

For example, an untreated splash of *o*-toluidine or hot *p*-chlor-aniline on the skin may in a few hours lead to the usual signs and symptoms of methaemoglobinaemia, followed by an intense haematuria as evidence of an acute haemorrhagic cystitis, which can be confirmed cystoscopically.

The vapour of 5-chloro-*o*-toluidine can give rise to a fulminating haemorrhagic cystitis, and is notorious on this account in the dyestuffs industry, outbreaks of this condition having occurred in a high proportion of workers in unsatisfactory plant and conditions.

Acute aniline intoxication of moderate degree can give rise to symptoms of bladder irritation and, on occasion, haematuria. The mild cyanosis (due to nitrobenzene or aniline) frequently encountered in workers on aromatic nitro and amino compounds is not usually accompanied by bladder signs or symptoms. But the number of workers in the organic-dyestuffs industry whose urine has at one time or another presented microscopic evidence of cystitis or of an irritant process in the bladder is high. The difficulty of following up the remote sequelae of such bladder effects lies not only in the fact that workers do not always remain in the industry, but also in the fact that they are not in general retained in the same process or operation, and so are exposed to a great variety of compounds.

Such compounds as α - and β -naphthylamine do not produce the acute symptoms of methaemoglobinaemia. Experimentally they do not do so even in very big doses, but benzidine, which is relatively very toxic, causes methaemoglobinaemia in the ordinary laboratory animals (not the rabbit, in which we have never been able to produce methaemoglobin with any agent). It is certain that, with benzidine, the daily absorption, which is enough to lead ultimately to a bladder tumour in man, is not enough to produce symptomatic cyanosis.

Cases such as those described by Muller (1933) must be very rare. These were 2 men, aged 22 and 34, who successively replaced another worker (engaged in grinding β -naphthylamine) who had developed bladder carcinoma. Each of these 2 men contracted severe haemorrhagic cystitis in a week. Cystoscopy showed extensive congestion of the bladder mucous membrane and isolated areas of necrosis, the latter a remarkable finding after so short a time of exposure. Both men recovered in a short time and were transferred to other work. The experimental analogue to Muller's cases is given by Bonser's (1943) dogs which, on a daily dose of 150 mg β -naphthylamine, developed haematuria in 3 weeks, and by Engel's (1924) dog which developed dysuria, frequency and haematuria in 2 days after subcutaneous injection of 0.8 g. β -naphthylamine. Whereas

Müller's cases may be presumed to have arisen from a massive and sudden absorption of the amine, other cases arise where, without any notable difference of working conditions, a sudden haemorrhagic cystitis makes its appearance.

One such case came to our notice in 1937, when a worker in a benzidine plant suddenly developed an acute haemorrhagic cystitis. The haemorrhage was such that cystoscopic examination was impossible. The bladder was inspected directly but no tumour was found; the bleeding was controlled and recovery was uneventful. No recurrences or signs of tumour in this patient have arisen in the intervening period of some 9 years. Engel (1924) refers to 2 cases of this kind among workers in β -naphthylamine and 1 case among workers in a naphthylamine and other products, all of whom developed papillomatosis in 2 or more years.

It is very difficult to determine the remote sequelae of acute haemorrhagic cystitis but our evidence seem to show that tumours do not develop from them. Reference has been made to 5-chloro-*o*-toluidine as a notorious bladder irritant. Our follow-up of a considerable number of men who had developed haematuria and other signs of haemorrhagic cystitis due to this compound and had recovered from them has not brought to light any evidence of tumour formation in the intervening 13 years.

A similar follow-up for 3 years of a case of violent haemorrhagic cystitis due to absorption *per cutem* of *o*-toluidine showed neither recurrence nor tumour formation.

It would appear almost as if the excitation of tumour formation by bladder irritants requires the latter to be (a) of the less violent kind and (b) to be exhibited in doses insufficient to lead to acute symptoms. In general terms, the tissue requires opportunity and time to react to the carcinogen, whereas the violent bladder-irritants break down the tissue reaction in its earliest stages. One of the most striking characters of these tumours is the furtive manner in which they develop, and another that they can arise long after all obvious exposure to the presumed carcinogen has ceased. The tumour-forming process, nevertheless, is at some stage accompanied or preceded by evidence of instability of the lining membrane of the bladder (flaking-off of epithelial cells) and/or of inflammatory changes (leucocytes) in the urine.

To obtain even a partial measure of the irritant action in the bladder is not possible. Analysis of urines of workers for aromatic amines shows great variations from day to day. It is usual to give "periods of exposure" but although we shall give some figures on this aspect the fact is that little precise significance attaches to them for one man may have as much real exposure in 2 years as another in 20 years.

A further factor in bladder irritation is personal idiosyncrasy. Some authors lay considerable stress on this and go so far as to consider that allergy plays a part (Hueper 1942) and offer this as a possible explanation not only of varying individual susceptibility, but also for the facts that a tumour may develop long after exposure has ceased and that frequently tumours develop after a primary tumour has been operatively destroyed and further exposure terminated. The suggestion is that a process of sensitization has become established and that it may be subsequently maintained by endogenous products formed in the body.

4 METABOLISM OF BLADDER CARCINOGENS

In the urine of workers in α - and β -naphthylamine it is usually possible to demonstrate the presence of diazotizable amine (a very small amount of colour-giving substances is normally present in urine i.e. on diazotization and alkaline

coupling with among other compounds R-salt). An increase in diazotizable amine is usually demonstrable after acid hydrolysis of the urine. Engel (1924) made the strange claim that whereas α -naphthylamine is in the dog partly excreted as base, β -naphthylamine is practically quantitatively excreted as 2-amino-1-naphthol.

Wiley (1938) fed β -naphthylamine to dogs and showed the presence in the urine of 2-amino-1-hydroxy-naphthalene conjugated with sulphuric acid. Dobriner, Hofmann & Rhoads (1941) injected rats, rabbits and monkeys with olive oil solutions of β -naphthylamine and showed the presence in the urine of the base itself its *N*-acetyl derivative its *N*-acetyl-6-hydroxy derivative and an unidentified dihydroxyaminonaphthalene.

Adler (1908) obtained from the urine of rabbits injected intraperitoneally with benzidine a dihydroxy derivative of melting-point 130-138°C.

In preliminary experiments with Hannon and Corby (unpublished) evidence was obtained by me that rats partly acylate benzidine and partly hydroxylate it in rabbits similarly treated with large doses of benzidine, the free base could be demonstrated in the urine. Using the method of chromatographic absorption and analysis of dyes prepared from benzidine workers' urine and comparing these with synthetic dyes made from various benzidine acyl and hydroxy derivatives, we have not been able as yet to demonstrate the presence of free benzidine or acyl benzidines.

In regard to aniline the older observations appear to be unassailed, viz. that this base is in part excreted as such in part as *p*-amino phenol (conjugated with H_2SO_4).

There is no certainty as to whether the direct carcinogens are the amino bases as such or metabolic derivatives of them but the negative point can be made that no suspicion has ever arisen of carcinogenic effects among the very many workers who have worked for years with a great variety of phenolic compounds as well as acyl and aryl derivatives of amines. Insofar as one would expect some common factor in the etiology of a disease such as this which whether arising from naphthylamines, aniline or benzidine, shows no great variations in its occupational aspects one is inclined to believe that it is the base as such which is the effective agent.

5 OCCUPATIONAL FEATURES OF THE DISEASE

a Manner of Absorption of the Amino-bases

The manner of absorption naturally depends upon the industrial conditions in which the hazardous operations are carried out. It is not improbable that in the latter part of the 19th and the first 20 years of the 20th century, workers in parts of the dyestuffs industry ingested *per os* considerable daily amounts of the solid amines and that absorption through the skin of especially aniline was far from negligible. In more recent years, with recognition of the nature and probable origin of the disease, absorption by these routes has probably been much diminished. Absorption by the respiratory route of the dust of the solid amines and the fume of all of them must have been very great. In the modern period this remains the most significant route and the one most difficult to eliminate especially at charging points, stills flaking- and grinding-machines drying-ovens sulphonators etc. Significant absorption can occur in non-manufacturing departments where contaminated materials are handled e.g. laundries repair-shops etc.

b Latent Period

This is the estimated period between the first entry into the hazardous occupation and the first appearance of signs or symptoms of bladder disease. It is a common practice among students of this condition to give average periods of latency. What precise meaning is to be attached to this average is not clear. The latency depends upon a number of factors, the weight of each of these being impossible to assess, e.g. individual predisposition, the intensity of exposure, perhaps the nature of the carcinogen, the continuity of exposure, intercurrent disease and perhaps still others.

Average latent periods recorded are

Oppenheimer (1927)	18.5 years
Büttner (1931)	17.5 "
Müller (1933)	17.4 "
Henschen (1937)	17.0 "

In my own series of cases the minimum latent period is about 4 years and the maximum 48 years. 53.6% of the cases had a latency of 11 to 16 years and 19.17% a latency of between 20 and 48 years. In Müller's series 42% of the cases had a latency of between 11 and 16 years and 28% between 25 and 36 years.¹

c Period of Exposure

This is the length of time during which affected workers are known to have been exposed to the hazards. It differs from the latent period in many cases, because the first signs of disease may appear years, often many years, after exposure has ended. No apparent relation exists between the period of exposure and the latent period, except that they are equal if work has been continuous and disease manifests itself whilst the hazardous work is still being pursued.

It is unusual for workers to be engaged without intermission solely in the hazardous processes and hence determination of the period of exposure is frequently approximate.

Koelsch (1935) held that 6 months' exposure to β -naphthylamine could be sufficient to lead to tumour formation. Hueper (1942) analyzed a European series of 137 cases, of which 47% had from 1 to 15 years exposure and 11.7% only 1 to 5 years.

Evans (1937) found that, of 83 cases in the USA, 13.3% had 1 to 5 years exposure, and 71% between 1 and 15 years.

In Müller's series (49 cases in which exposure period could be given), the shortest period was 1 year and the longest 37 years. 50% had from 1 to 15 years and 32.7% had from 26 to 37 years. G. di Maio (1937) examined 86 dyestuffs workers and found that 26 had "pre-cancerous" changes, 7 had benign and 4 malignant tumours in the bladder. The periods of employment in the industry were 2 to 6 years in the "pre-cancerous" cases, 3 to 9 years in the benign cases and 6 to 15 years in the malignant cases.

In my own series the precise total period actually worked in the hazardous process was indeterminable. The only reliable figure was the total period in the industry before development of a tumour, and clearly this will in many cases be considerably higher than the actual period of exposure to the hazards.

The shortest period thus determined was 3½ years, the longest 33 years. Of the 54 cases, 48% had from 3½ to 19 years in the industry and 13% had from 26 to 33 years in it before developing bladder disease.

Other data in the literature substantiate as a fundamental feature the fact that the disease may become established in

a very short time and that, therefore, medical observation and urinary or cystoscopic control are necessary from the start.

d The Affected Worker

Assuming that treatment of the affected worker has been sufficiently successful to permit of his return to work, the question at once arises whether he should be returned to his former occupation. The natural and immediate response is likely to be in the negative, but various reasons can be given against such a view, and may be summarized thus:

- i If the hazard still exists, replacement of the worker will increase the population at risk.
- ii The affected worker, even if apparently cured, is still subject to the possibility of recurrence whether further exposed or not.
- iii If cystoscopic control is practised, recurrence can be detected at a stage early enough to be reasonably assured of successful destruction of the tumour or tumours.
- iv With improvement in plant-construction and -operation the hazard is being steadily overcome.

The reaction of the worker to each of these may be rather different and may often be summarized thus:

- i This argument is not very impressive to an affected person.
- ii Is it as likely that recurrence will occur in non-hazardous work as in the former work?
- iii Since cystoscopic control should continue in any event, why not return to the hazardous occupation? (This is not infrequent among the more intelligent workers but depends on his experience of and reaction to cystoscopy.)
- iv What special improvements have been introduced and what special amenities and safety-precautions are now available? The lag between improvement in conditions and any fall in incidence is obvious.

The practice recommended by American authorities (notably Gehrmann, 1936) is to return the men to the former work. In recent years the Swiss industry has followed the same practice (Müller, 1945), and it is recognized by the Swiss National Accident Insurance. German authorities recommended the practice a good many years ago, although Nassauer (1919) went so far as to recommend 3-monthly change in personnel. In Britain it is difficult to be sure what the practice is. The disease is not scheduled as an industrial disease and no regulations have been issued as to the course to be adopted. The writer takes the view that the particular circumstances of any individual case must determine what is recommended. Had Simon's (1930) view of the relatively benign character of these tumours been borne out by experience, the issue might have been easier to decide, but it is now known that they are very often extremely malignant. In a high proportion of cases, return to work of any kind is impossible. In others, for example, after considerable resection, a long convalescence is often necessary, and return to the routine of a chemical process is not considered by the patient. Cases successfully treated by fulguration, especially if the tumour has been located in the vault, frequently look and feel well and can return to their former work but have little desire to do so.

The psychological effect of a severe haematuria cannot be neglected in some workers. Instances are known of men refusing to continue to work in a process where cases of bladder disease have been detected.

The dilemma can be resolved only by such redesign or reconstruction of plant and control of atmospheric conditions, and by elimination of all handling of the products—

¹ The dilemma presented by data of this kind is apparent in that, given industrial and individual conditions which may provoke the disease, there does not appear to be any certainty that the disease will not be established even after leaving the industry. In spite of this, however, it is by no means the case that all exposed workers develop the disease. It has been stated that it is mainly workers of unclean habit who are most prone.

or better still, by the rejection of routes of manufacture which involve the separation of the carcinogenic bases—that all workers can be assured of the safety of the work. The writer is not unaware of the difficulties

e Factory Medical Control

i Prospective employees who are to enter the hazardous processes should

- a be healthy adults and of clean habit
- b have no family history of malignant disease
- c have no personal history of renal or vesical disease
- d have no history of venereal disease
- e be given a cystoscopic examination before commencing work and be rejected if any sign of disease is present
- f agree to periodic routine cystoscopy at least once a year

The age at which such workers should be permitted to enter the hazardous work depends in our view on the conditions in the particular factory. Judgment should be based on the loss of expectation of life hitherto experienced by affected men in the industry. Where the working conditions are bad the loss of expectation of life is worse for young men than for older men. If the object in employing a worker is to assure him of a reasonable length of working life then subject to the requirements given above he should not be permitted to enter this work as a young man unless the conditions are held to be substantially safe.

Those who recommend that young healthy men should be chosen for this work may not have had our experience of the effect of successive cystoscopies on the minds of young people.

ii Prospective employees should be informed of the nature of the work and instructed in detail of the hazard involved and the measures to be taken to combat it.

iii Once allocated to a hazardous process the worker should if possible be maintained there throughout his working life.

iv Throughout his working life he should be under medical control designed to detect any sign of incipient or overt disease of the bladder. Such control should include full clinical examination every three months, laboratory urine testing (chemical and microscopic) and cystoscopy at such periods as appear to be dictated by the working conditions e.g. in poor working conditions 6-monthly cystoscopy may be considered necessary. Chemical tests on urine should include determination of urinary aromatic primary amines as a check upon the working conditions.

Maintained presence of abnormal cell constituents in the urine should lead to cystoscopy. Routine cystoscopy is stated to be used in USA and Switzerland but not in Britain. The great advantage of routine cystoscopy is that it is more likely to detect tumours before malignant changes have developed and in a small proportion before any urinary signs are present.

Valuable as routine cystoscopy is its practicability is dependent upon the acquiescence of the workers. In the USA cystoscopy, in certain industries, can be performed in the factory medical department.

6 LEGISLATION

Whereas in some countries the disease is notifiable and scheduled as an industrial disease this is not as yet the case in Britain.

The difficulties inherent in the problem of schedule, in the manner adopted in Britain of a condition such as bladder tumour are so great that in spite of the tacit recognition of

it as an occupational disease for many years, a practicable formula has not been found. Not least among the difficulties are those of making allowance for the latent period and of making a reasonable specification of the processes which would be held to involve the hazard.

A very great difficulty is to define when the disease is to be held to be present. The pre tumour stage is an elastic conception, but it would not be equitable to define the disease only on the detection of an overt growth. Further since in a few cases renal tumours have been present with the bladder tumour it would be impossible to delimit the disease to the bladder alone. Again nobody would be ready to assert that a known liability to tumour-formation in the bladder would be without some influence on organs or tissues in the neighbourhood of that organ.

The absolute incidence of bladder tumours in the population as a whole is considerable and since aromatic amines or their derivatives are used in a variety of industries it becomes still more troublesome to find a reasonable formula.

It is conceivable that a restriction to certain occupations might be practicable but the period during which an employer or other source of compensation should be held to be liable could not be less than the lifetime of the worker.

Since it is known that a liability to recurrence is a feature of the disease even without further exposure to the hazards the right could not be denied for an affected worker to claim a damage done to him which will last for his lifetime. The repercussions of such a right need hardly be emphasized.

It may perhaps be practicable to draw up registers for all persons employed in particular processes and apply the provisions of a special schedule to them and to them alone. This combined with the most stringent regulations as to the design and operation of plant working conditions and medical control might go some distance in eliminating the disease. The duty of deciding as to the occupational origin of the disease in any given case could be made to lie upon the medical control and upon a person or persons appointed by the appropriate minister. In the event of death due to the disease the medical control and its detailed records could be made available to the coroner and the persons appointed. Retrospective cases would each have to be considered on their merits.

7 SIGNS AND SYMPTOMS

It may be said at once that there is nothing to distinguish between the signs and symptoms of the occupational tumour of the bladder and those of the non-occupational. The outstanding difference lies in this that there is ample knowledge on some aspects of the causation of the former and a reasonable chance of anticipating the worse forms if routine cystoscopy is adopted.

There is a greater or lesser length of time during which no external signs or symptoms at all are present, but even in this period a tumour may already become established. The period of no external signs or symptoms may be terminated by a sudden haematuria with little or no discomfort or pain, this may be due to a tumour.

On the other hand it may end with the appearance in the urine of epithelial cells and later a few erythrocytes but still without symptoms. Examination of the bladder at this stage may show little significant change. Maintenance of epithelial exfoliation and slight haematuria may be found later to be associated with a slight ulceration or a tumour. From the first appearance of haematuria to the demonstrable

presence of a tumour, a very considerable time—even years—may elapse. Throughout this development, the general condition of the patient is usually quiet and undisturbed, so much so that he may refuse cystoscopy until visible haematuria convinces him of its necessity.

No certain relation appears to exist between the degree of haematuria and the degree of malignancy of the tumour. Nor need even a considerable haematuria be certain evidence that a tumour is present, as has already been pointed out. Cases are found in which no symptom is complained of except a certain amount of "backache", and in which the urine shows a maintained slight haematuria with associated leucocytes, and yet an inoperable carcinoma is discovered on cystoscopy. On the other hand, a sudden severe haematuria may be found to be associated with two or three small papillomata not as yet showing obvious malignancy. Thus, the detachment of a frond from a highly friable "benign" villous papilloma may be followed at once by violent bleeding, on the other hand, an ulcerated sessile papilloma with considerable invasion into the bladder-wall may show a similar violence of bleeding, whereas an exactly similar tumour with marked malignant changes in the base, but little breakdown at the surface may show no visible bleeding or only microscopically detectable blood cells. One sometimes has the feeling that a considerable haematuria is more likely to turn out to be due to a papilloma of good prognosis.

The intensity of the haematuria may vary greatly from day to day, sometimes ceasing altogether for weeks or months at a time. Such cessation is no indication of any diminution in tumour development. It may lead to a belief in the patient that the condition is disappearing but will not deter the surgeon from maintaining his cystoscopic examinations. Leucocytes are often found in the urine of workers affected by tumour of the bladder, sometimes in considerable amount. On the whole, the likelihood of malignant change is greater if much pus is found, assuming that instrumentation or operation or the usual causes cannot account for it (descending infection, pyelitis, obstruction, prostatic disease, gonococcus, etc.). Leucocytes indicate, in general, ulceration either of the lining of the bladder or of the surface layers of a tumour, and they need not be associated with pyogenic organisms unless there is obstruction.

Haematuria may lead to formation of thrombi, and the passage of these results in great pain on micturition, acute retention has also been observed. Similar symptoms may follow dislodgement of small masses of tumour tissue, such small masses, sometimes in the form of fluffy threads, are often seen in the urine.

The degree of pain in malignancy depends also upon the infiltration and invasion of the bladder-wall and of pelvic tissues. A worker may seek advice for pains in the "bottom of the back" or the supra-pubic area, or even vaguely in the hypogastrium, before there is any apparently significant haematuria, and a deeply infiltrating tumour may be found. At a late, almost terminal, stage, when the branch systems from the pelvic plexus are also involved, maintained pain is present. When this has occurred, there is almost certainly an associated pyo-nephrosis with pain in the lumbar region.

It is unusual nowadays for a case of operable papilloma with haematuria to be allowed to proceed to a state of secondary anaemia, but the inoperable case, carcinoma or

papilloma, soon deteriorates, the patient developing toxæmia and all its sequelae in spite of deep x-ray therapy or implantations of radon.

8 PATHOGENESIS

Writers on this disease commonly emphasize that the most frequent location of the tumours is in the trigone and in the region of the ureteric orifices. This fact is adduced by some in support for the view that the tumours arise from the effects of the carcinogenic agents excreted in the urine and maintained in contact with the base or trigone in greater quantity and for longer periods than elsewhere.

The evidence in favour of this relative stasis as an important factor is mainly from experiments in dogs, in which the majority of the tumours induced were found in the dome and in the anterior parts of the bladder, where also the biggest tumours were present—i.e. in the most dependent parts in the ordinary lying or standing attitudes (Hueper *et al.*, 1938). A similar position is found with tumours induced in mice by oestrogens, in rabbits by β -naphthylamine, and in dogs by aniline and *o*-amino-azotoluene (Lacassagne, 1935, Yamazaki & Sato, 1937, Hueper *et al.*, 1938).

Again, the facts that the attack in the bladder is primarily on the epithelium and never on the connective tissue, and that the tumours formed are epithelial tumours and not connective-tissue tumours (sarcomata), would seem also to point to a direct action on the lining of the bladder, unless it can be shown that the carcinogens are in some way specifically active against epithelial tissues.

Some importance attaches also to the fact that the solubility in the urine of both the amino-bases and their metabolites will diminish as the urine pH increases: the resulting undissolved matter will then tend to accumulate on the base of the bladder in man.

Structural abnormalities predisposing to stasis of urine in the kidney should, on the view that the amino-base is the carcinogen and acts from the urine, bring about conditions likely to lead to tumour formation. Cases of this kind have been described. Thus Muller (1936) reported a case in which, 6 years after partial cystectomy for carcinoma of the vault in a benzidine worker, there was a recurrence of haematuria which was shown, after much investigation, to be due to a carcinoma in a supernumerary kidney on the left side. The tumour was considered to have arisen in the pelvis of this accessory kidney, it had involved its whole mass, and had pushed a plug of malignant tissue into almost the whole length of the ureter. There were two ureteric orifices and two parallel ureters on the left side. The other kidney lay below the tumour-bearing one, was compressed, and was apparently functioning normally. There was no recurrence in the partially resected bladder, and hence the renal tumour was taken to be a new primary growth. It was very malignant and had given rise to many metastases. The known liability of double kidneys to stasis and disease suggests itself as having some relation to the tumour formation, in that the amino-base or its derivatives would have been longer in contact with the supernumerary organ than was the case with the normal kidneys.

In addition, experiment can readily show that injection of amino-bases of the kind associated with this disease are rapidly concentrated in the bladder and continue to appear there for longer than they do in the other principal organs and tissues.

* It is significant to recall that Debenham (1933) from a study of 742 cases of haematuria concluded that when this occurs as the initial sign in the male, there is a 50% chance that it is due to carcinoma of the bladder.

On the other hand, Ferguson, Gehrmann, Gay, Anderson & Washburn (1934) proposed the theory that the carcinogenic action was exerted not by the products when in the urine, but as they circulated in the blood. In support of this there were the following observations: the tumour-forming process appears to begin as a sub-epithelial vascular reaction, the epithelium being affected secondarily, any part of the organ may be involved, the much greater vascularity of the trigone, the so-called recurrences are almost certainly newly-arsen tumours, routine cystoscopy frequently shows localized sub-epithelial telangiectasis and blood effusions.

Schär (1938) held, on experimental grounds, that the carcinogen

- i circulates in the blood and hence in the vesical vessels,
- ii is excreted in the urine and is therefore in contact with the epithelium,
- iii can be excreted into the bladder by diffusion from the vessels,
- iv can be re-absorbed from the bladder and be deposited around the capillaries in the bladder wall

Schär's hypothesis combines features of the two others, but adds the conception of re-absorption from the bladder, for which substantial evidence exists, especially if the bladder epithelium is congested or inflamed. These theories do not offer a real explanation of the fact that tumours may and do develop long after all exposure has ceased, or of the long latency during exposure, or of the apparent immunity of many workers. It seems to us that no simple theory of the carcinogenicity of the amino-bases can explain the appearance of tumours years after the last trace of them must have disappeared from the body.

On the grounds of location and nature, there is no fundamental difference between the occupational and non-occupational tumours. Even Hueper (1942), who is a protagonist of the urine-carcinogen theory, agrees that "bladder tumours of chemical etiology follow in their location and distribution the cryptogenetic vesical neoplasms". Recent work by Steele, Koch & Steiner (1941) and Shabad (1945) offers evidence of the existence in urine of so-called blastomatogenic agents.

One is tempted to consider that both groups, occupational and non-occupational may arise from the same ultimate process. On such a view foreign substances such as the aromatic amino-bases or their metabolic derivatives present in the blood or the urine, may act as potentiators of the tissue or of the process.

The presumption is that the carcinogen is present in greater or lesser degree in all but that the tumour reaction will depend on the sufficiency of the carcinogen or on that of the potentiator. Such a hypothesis could perhaps account for the marked tendency to "recurrence"—i.e. once potentiated, always potentiated.

Again, different individuals may be held to have varying amounts and availability of carcinogen and hence, even with the same amount of potentiation, varying response from none to extreme malignancy (This is, of course, known among workers in amino-bases). The relative incidence of occupational bladder-tumours among young adults is much in excess of that of non-occupational tumours. This fact on the above hypothesis, may be due to a marked potentiation of otherwise unsufficiently active carcinogen.

The identity of the two groups of tumours suggests some identity of process. The practically exclusive incidence of

the disease in the bladder suggests that potentiation is dependent upon adequate concentrations.

The conception of potentiation is familiar in physiological and pharmacological processes and in allergic reactions. In industrial skin disease, especially that associated with exposure to organic compounds it is very common to find a general potentiation of the skin (polyvalent sensitization) arising from an apparently quite trivial local reaction to an irritant compound.

To regard the aromatic amino-bases as potentiators simply splits the problem of causation. The fact that these compounds can by direct action produce manifest injury to the bladder lining is not the sole basis for the conception for many other organic compounds also can injure the epithelial lining without as far as we know leading later to tumour formation. Inflammatory disease of the bladder lining is clearly not a necessary precursor of neoplastic growth. The old calculus theory of bladder tumours was long since exploded.

The problem is clearly more subtle. The key lies we suggest in discovering first what structural or functional changes are brought about in the bladder epithelium by the presence of the amino-bases or their derivatives. One of the changes brought about already referred to is a disruption of the stability of the layers of epithelial cells.

The second necessary point to elucidate is the endogenous factor which, acting upon an epithelium which is attempting to regenerate, produces that extra stimulus which in the issue is carcinogenesis.

Selection of organs for attack in cases of non-occupational neoplastic growth is always a puzzle. In occupational tumours the selection is perhaps less of a puzzle, because of the close correlation between the point of attack of the occupational hazard and the location of the subsequent primary tumour development. But we hold that the evidence points to the existence of some unitary process. Multiplicity of carcinogens as at present understood without the belief in and search for underlying unity is chaos.

9 PATHOLOGY

The tumours benign or malignant that arise as a result of exposure to amino-base are epithelial growths. The changes other than neoplastic that arise are changes in the epithelial lining of the bladder.

Although a considerable variety of appearances is found the principal are

papilloma (apparently benign), papilloma and carcinoma, papillary carcinoma, nodular infiltrative carcinoma of the bladder.

Of much less frequent occurrence are mucous polyps carcinoma of the renal pelvis carcinoma of the ureter adeno-carcinoma of the bladder leukoplakia.

A picture of the development of the tumours is obtained from the experimental results of Hueper *et al* (1938) and Bonser (1943). The latter saw gradation from simple epithelial hyperplasia to carcinoma with lymphatic permeation and invasion of muscle. The epithelial layers increased in numbers and the cells were swollen.

Further there were intra-epithelial proliferation with down-growth into the sub-epithelial tissues: this downgrowth was stated to have been of both simple and malignant character. Simple and malignant tumours were found, the former, simple transitional-cell papillomata with characteristic papillary fronds the latter, malignant papillomata of transitional-cell type, of

anaplastic polygonal-cell type, and of tubular type any malignant tumour might be of mixed type

In the histologically benign papilloma Hueper *et al* (1938) noted that the cell layers on the papillae varied in number from 2—3 to 20 or more. The cells appeared to be of normal transitional type, but on occasion were hyperchromatic and almost lymphoid, and sometimes large polygonal and of epithelial type. The vascular connective tissue of the core of the papillae appears loose and oedematous, and moderately infiltrated with lymphoid and mononuclear cells. The capillary network is rich and dilated, and at the tips of the papillae small haemorrhagic areas are seen. Degeneration changes in the epithelial cells included ballooning, cytoplasmic vesiculation, nuclear pyknosis, atrophic shrinkage, and intra-epithelial cyst-formation. The pedicle could undergo fibrosis. The papilloma could assume a variety of shapes and consistencies, from the tufted delicate fibro-epithelial type to the stumpy, thick, sessile warty projections. Multiple small papillomata narrowly separated were also found, constituting the condition of papillomatosis.

The potentially malignant changes which an apparently benign papilloma may undergo are common experience, and may in man follow unsuccessful attempts at destruction. So long as a certain regularity of structure is maintained, e.g., long axis of epithelial cells at right angles to long axis of papillae, the benign character is at least likely to be preserved, but when there begin to appear groups of irregularly dispersed and irregularly shaped cells with frequent and abnormal mitoses, it is certain that malignancy is developing. In the region of or in the base of the tumour, invasion into the wall of the bladder begins and, unless destruction is successfully performed, proceeds more or less rapidly to involve the whole thickness of the organ and beyond. When this invasion has become well established in the wall, fulguration often fails to prevent extension or recurrence.

Whereas malignant changes can set in upon a papilloma which in favourable circumstances might have remained benign, in many cases the process appears to have been malignant from the start. The individual factor is very evident, for whereas some workers will repeatedly present tumours which are apparently entirely benign, others seem never to have gone through a period of benign growth but react with malignant invasion from the outset of the tumour formation. The process may be mainly centrifugal or centripetal in relation to the lumen of the bladder. In the latter case, a papillary carcinoma is the likely result, in the former, a nodular infiltrating carcinoma. Papillary carcinoma arises on a broad base, or a broad base may develop from the coalescence of neighbouring papillary projections. The tumour in its early stages may be seen as a slightly elevated plaque which more or less rapidly develops into a solid round-topped mass, sometimes short villous processes are seen from which, if there is ulceration, there may be considerable bleeding. Malignant invasion occurs into the fibro-vascular tissue and into the bladder wall adjacent to the base. Histologically, balloon cells, giant cells, active mitoses, and local necroses are seen. The latter may be associated with atelectasis of the capillaries or with infection. Experience in clinical control of workers leads one to lay considerable stress on the presence of leucocytes in the urine as an accompaniment of probable malignancy. This type has been stated above to be mainly centripetal in growth, extension through the bladder wall does, of course, occur, but in many cases this process is relatively slow.

In the nodular infiltrating carcinoma there is early invasion of the sub-epithelial layer by abnormal pegs of cells similar to transitional epithelial cells. Frequently the cell-type is undifferentiated and may be round or oval, giving a sarcoma-

like appearance. The tendency to liquefaction-necrosis may yield an appearance of adeno-carcinoma, but true tumours of this kind are rare.

The nodular carcinoma may arise from a leukoplakic area of irregular, swollen vesicular polygonal cells lying on deeper layers of transitional cells.

Involvement of the ureters and kidneys is unusual but is described. In our experience tumours of the ureters have appeared to be extensions from the bladder tumour.

Muller (1940) described an interesting case in which there was a broad-based typical transitional-cell papilloma in the ureter below the point of crossing the common iliac artery, associated with intense inflammation of the ureteric wall. This tumour was considered to be primary. It was discovered by operation from which there was recovery. In our experience, involvement of the ureter has occurred quite close to the ureteric orifice has been malignant, and was discovered post-mortem, in one case it was bilateral. In the rare cases in which the kidney was involved, the tumour, in our experience, was primary, was of the infiltrative type, and was diffused throughout the organ, which had been almost completely destroyed. In one case there was a metastatic nodule in one kidney secondary to a very extensive sessile infiltrating carcinoma of the bladder, large metastatic deposits in this case were found in the lumbar lymph-glands and in the mediastinum which, on section, proved to be transitional-cell carcinoma. Primary tumours of the renal pelvis have not been found in my series.

Metastases have been described in the regional, inguinal, and paravertebral lymph-glands, in the latter case as high up as the cervical spine. The supraclavicular glands may be involved. In one of our cases there was a large gland-mass on the left neck. Perirenal metastases may extend to and perforate the lumbar skin (Muller, 1933). Others may be found in vertebrae, liver, lungs and even in the cerebrum.

Direct extension of the tumour may involve the sigmoid colon and on occasion the prostate. The ureteric orifices on one or both sides frequently become occluded by an extensive growth and, on occasion, the ureter itself becomes occluded by the infiltrated tumour. The consequences of such effects—hydro-nephrosis, pyonephrosis, infection, dilation and accumulation of pus in the ureter, toxæmia—are manifest.

10 TREATMENT

a Prophylactic Measures

Since the workman exposed to certain aromatic amino-bases is undergoing a process which sooner or later may lead to the formation of a bladder tumour, it is logical to prescribe treatment from the beginning of exposure.

On the hypothesis that the concentration of the compounds excreted in the urine is a determining factor in the stimulus to tumour development, increased fluid intake may be prescribed, e.g. 3 or 4 pints [1.7-2.3 l.] of milk, coffee, tea or other non-alcoholic drinks and a diuretic during the working-day or -shift. The volume of fluid thus given should be sufficient to reduce the concentration of diazotizable amine in the urine to almost indeterminable levels.

On the hypothesis that the active agent is the amino-base, it may be helpful to assure that the urine is maintained always on the acid side. Hence the administration of adequate amounts of such compounds as sodium hydrogen phosphate, calcium chloride or ammonium chloride, and an "acid-forming" diet is indicated.

Attempts to inactivate the amino-group by the administration of non-toxic chemical compounds suggest themselves, but we have not succeeded in finding a suitable agent.

The frequency with which workers are found to have a low-grade cystitis suggests that a urinary antiseptic may have its place in these preventive treatments.

The absolute amount of diazotizable amine in the urine (before and after hydrolysis) can serve as a useful control on the plant conditions

b Acute Haemorrhagic Cystitis

Acute haemorrhagic cystitis brought about by the absorption of aromatic amines is treated on standard lines of rest in bed, bland diet and bladder-sedatives and diuretics. Symptoms are sometimes quite severe but we have found these cases to clear in 2-4 weeks. Once removed from the chemical source, there is a rapid diminution of the haematuria and symptoms.

In some cases however, the acute form may pass into a chronic but mild form not associated with tumour development. Operation or instrumentation can contribute to the development of the chronic form. This is illustrated by the following case.

A man of 33, who had worked for 5 years in chemical processes without any urinary signs or symptoms was transferred to a benzidine process where he worked for 2 years without any urinary abnormalities. He then suddenly developed in extremely violent haematuria with pain, frequency and strangury. A very complete examination showed no renal disorder and only an intense inflammation of the floor of the bladder. As the haemorrhage was very profuse, the bladder was opened, but no tumour was found. The urine was bacteriologically negative (including guinea pig test). A period in hospital and mild treatment led to recovery. The patient returned to work and was set to boiler-firer which he pursued for 8 years. There has been no further contact with hazardous compounds. During this period he has had 28 urine examinations and 1 cystoscopy. The latter, some 2 years after restarting work was quite negative, but there have been intermittent mild haematuria and pyuria on one occasion 5 years after the operation there were many erythrocytes seen in the urine. At present, 8 years after operation, he is well and, except for a faint albuminuria free from all signs or symptoms of bladder or other disturbances.

c Surgery

The surgical treatment of occupational tumours of the bladder is the same as that for non occupational. According to the circumstances of the case transurethral or endovesical high frequency electro-coagulation partial cystectomy (with or without electro-coagulation) implantation of radon seed (with or without electro-coagulation), deep x-ray therapy or total cystectomy after implantation of the ureters are practised.

1 *Electro-coagulation* of a tumour in the benign stage or in the stage of superficial, non-infiltrating malignancy is usually followed by good recovery. Transurethral approach may be rendered impossible by the location of the tumour or by its size or multiplicity. Even in the best conditions, without any further exposure to the hazardous compounds the possibility of new formations later remains. This character of new formation applies to non-occupational as well as occupational tumours of the bladder.

After successful electro-coagulation the patient may remain free from further tumours for the remainder of his life. Perhaps the likelihood of new formations is greatest in cases where there have been multiple tumours even benign at the first operation. An example of this is given by the following case.

A man of 48 having worked for 14 years in a variety of processes, including 12 years in contact with β naphthylamine was found to have 2 small papillomata to the right of the right ureteric orifice 2 on the fundus and 1 on the anterior wall of the bladder. Transurethral coagulation was performed in June 1936. In April 1937 cystoscopy showed freedom from

tumours, but the vessels round the internal urethral orifice were dilated and haemorrhage could be seen from various points on them. From October 1936 till January 1940 he worked in the open air and was then transferred to laboratory work associated with the β naphthylamine plant, where he worked till April 1944. In July 1940 slight signs appeared, but the patient consistently refused all investigation or treatment. This situation continued until February 1945 when it became obvious to him that he was ill. In August 1945 an inoperable carcinoma involving the base trigone and posterior wall was diagnosed cystoscopically, both ureteric orifices being obstructed by growth. The post mortem in February 1946 showed bilateral pyonephrosis dilated and pus filled ureters and an extensive papillo carcinoma in the bladder.

Ineffective coagulation of even an apparently benign papilloma may be followed by rapid growth and establishment of malignancy.

Cases of frankly malignant tumours will not benefit from high frequency treatment except perhaps when the growth is very small. Indeed, it is not improbable that such treatment may in such cases make matters worse. Attempts at coagulation of malignant tumours are often followed by introduction of radon seeds either because of doubt as to complete destruction or as a precautionary measure.

Electro coagulation after cystoscopy is often necessary, particularly when there are multiple tumours. The danger of release of viable tumour-cells and their later implantation is perhaps greatest in this method.

ii *Partial cystectomy*, if the tumours are suitably located can yield good results.

Thus, a man aged 55 years who had worked with a naphthylamine for 15 years was found to have 4 small papillomatous and pre papillomatous areas in widely separated regions of the bladder. Treatment by electro-coagulation was followed in 6 months by the appearance of a papilloma $\frac{1}{2}$ inch [8.5 mm] diameter, in the vault its surface was necrotic. The location of the new formation did not permit of transurethral treatment. A partial cystectomy, using the cautery knife, was performed and recovery was good. The patient returned to work some months later and has continued out of contact with chemical products of any kind for 8 years. Several cystoscopic examinations have revealed only a basal cystitis. Urine control continues. Some 4 years after operation, the urine began to show a heavy content of pus and some erythrocytes. At various times, attempts were made over prolonged periods to overcome this cystitis with hexamine, sulphonamides and mandelic acid, but with no success. The patient now in his 63rd year has been continuously at work (non-chemical), looks and feels well, and has increased considerably in weight.

Muller (1933) was able to resect in 5 cases of occupational carcinoma of the bladder (vault and anterior wall), of these 2 had already survived 8 years at the time of reporting and were able to carry on their work.

Resection should be preceded by complete destruction of the tumour or tumours and a wide area of normal bladder wall surrounding the tumour should be included in the resection.

Where resection is the chosen operation and a ureteric orifice is surrounded or invaded by tumour-growth, it becomes necessary to remove this area and re-implant the divided ureter into the posterior wall of the bladder.

Opportunity for this operation arose frequently in our series of cases, but there appears to be some reluctance in regard to it on the part of some urologists. Beer (1935) stated that "fear of sacrificing the ureteral ostium has undoubtedly led to many deaths as the surgeon has failed to do a radical excision." It must of course be first determined that the kidney on that side is in good function but Beer with his very extensive experience stated that the only indication which I can see for a nephrectomy at the

time of the primary operation is a badly infected kidney with a very large dilated, diseased ureter, and that only in case the second kidney has been shown, by excretory urography, to be adequate."

Beer's analysis of his operative results on 137 cases of infiltrating, ulcerated, solid, more or less papillary carcinomata may be summarized as in Table I

TABLE I

No of cases	Operation	Operative mortality	Remarks
67	44—Resection 23—Resection and sacrifice of ureter orifice	27% } 21% } 25%	34% were "cured" (Periods of observation from 1 to 16 years, 3 lost to follow-up)
55	Electro coagulation and radon	18% immediate 27% died within few months	12% were "cured" (Periods of observation from 1 to 12 years, 9 lost to follow-up)
15	Deep electro-coagulation	40% (operative and soon after operation)	No "cure" reported (4 recurred, 1 lived 2 years, 1 recurred in 5th year, 3 lost to follow-up)

Statistical comparison is impossible with such data, but it appears fairly certain that resection for tumours of this malignant kind is the operation most likely to succeed.

iii. *Total cystectomy* Consideration of malignant growths which are not susceptible to any of the above procedures, results in a gloomy picture. Deep x rays and radon-seed implantation may retard the inevitable sequel. X rays may diminish the size of metastases, but we have not seen any maintained improvement. Provided there is no renal damage and no extension of the malignant process into the pelvic structures, the question of total cystectomy must be considered in the otherwise inoperable case.

Ward (1936) considers that it is "far better to risk an operation which, if successful, will give relief rather than drag out such a miserable existence" as is the inevitable sequel in an inoperable case.

Not the least of the difficulties encountered is to convince a workman of the desirability of the operation before the condition has advanced too far to offer any chance of success.

The fact that recurrences (new formations) are so frequent has led urologists experienced in occupational bladder tumours to regard total cystectomy as indeed the only rational operation. This is perhaps rather an extreme view, for in the occupational variety, as has already been stated, there is a possibility of the recognition of tumours long before the inoperable stage has been reached, and this signifies routine cystoscopy of all workers who have been or are being exposed to the hazards. There is in Britain a considerable number of workers to whom this should apply if the inoperable situation is to be avoided. No doubt a certain proportion will be found to show a primary infiltrating growth which will not respond to measures less radical than

total cystectomy, but a high proportion will be amenable to such measures.

11 SURGICAL PROGNOSIS

Washburn's analysis of his cases (1934, 1937) shows that in 50 of 86 diagnosed cases there was a small tumour amenable to fulguration. Gay's (1937) examination of 93 specimens from 61 workers who had been in the dye industry for 5 years or more showed that 50% were benign, but it was pointed out that such tumours could, in time, become malignant. No doubt these findings are related to the practice of routine cystoscopy with consequent early diagnosis.

It is to be recalled that Simon (1929) reported his series of 81 "aniline" cases as all histologically malignant. Only small tumours were electro-coagulated, extensive resection being the method most frequently used. Many of these cases underwent repeated resections in the course of years. Of the 29 cases still alive in 1928, 15 had survived operation by at least 5 years and 17 by at least 3 years (total number operated 35). Of the 52 cases dead up to 1928, 37 had been operated on, 8 had survived at least 10 years, 16 at least 5 years, and 21 at least 3 years. Having regard to the effects of advancing years, and causes of death other than bladder disease, Simon's results indicate early diagnosis, especially as the tumours were all stated to be histologically malignant. Simon does not appear to refer to such a thing as an inoperable case. In our two series of occupational cases, it was found that, of 12 cases in the first series, 2 were inoperable, and, of 45 cases in the second series, 7 were inoperable at the time of first coming for treatment, i.e. about 16%.

When, as in non-occupational cases, early diagnosis of cancer is the exception, complete excision of the tumour is possible in only a minority of instances. Thus, in a study of 902 epithelial tumours of the bladder listed in the Carcinoma Register of the American Urological Association (1934), it was found that from the standpoint of surgical treatment, only 23.4% were readily accessible for complete excision without interference with the ureter or urethra. Thus, in non-occupational carcinoma of the bladder, the American surgeon has to reckon with some 76% of cases for which he will have to consider re-implantation of the ureter after resection or total cystectomy.

In Beer's series (1935) of 650 cases of treated bladder tumour, 36 papillary carcinomata were treated by electro-coagulation and resection, with apparent cure of 69% of those not succumbing to the operative procedure, 67 infiltrating and ulcerating carcinomata were similarly treated with 50% cure, 42 papillary carcinomata were treated by transurethral electro-coagulation with 54% cure, and 18 cases of infiltrating, solid carcinoma were treated by total cystectomy, with 46% cure of those surviving operation and followed-up. The operative mortality in the last group was 28%. Beer held, on his results, that radical excision or total cystectomy offer not only a more complete eradication of the disease but also a better proportion of cure among those who survive the operations. The problem is to reduce operative mortality.

In the case of occupational bladder tumours, the operation of total cystectomy and implantation of the ureters into the skin (Beer) would appear to be impracticable for a workman who, if he recovers, can find little to do to make life worth living. It would appear that the only reasonable chance of making it possible, if cure is attained, for the patient to

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Attempt the end and never stand to doubt
Nothing's so hard but search will find it out."
Herrick

NOTE ON THE CHEMOTHERAPY OF CANCER

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- 1 General
- 2 Synthetic oestrogens
 - a. Effects of castration in cancer of the prostate
 - b. Influence of oestrogens upon cancer of the prostate
 - c. Histological alterations due to the administration of oestrogens
 - d. Mode of action of oestrogens upon cancer of the prostate
 - e. Ovarietomy and oestrogens in cancer of the breast
- 3 The β -chloroethylamines
 - a. Cytotoxic and nucleotoxic effects of the chloroethylamines
 - b. Possible modes of action of the chloroethylamines and sulphides
 - c. Experimental and clinical applications in chemotherapy
- 4 Action of urethane in leukaemia
 - a. Effects of urethanes upon animal tumours
 - b. Clinical effects in leukaemia in man
 - c. Possible modes of action
- 5 Conclusion
- References

1 GENERAL

It was Sydenham who said, "I have often thought, that if I knew accurately the natural history of any disease, I should never be at a loss for a proper method of treating it." This must be our text, or justification, for including a note upon chemotherapy in a symposium devoted to carcinogenesis.

Until the latter part of the nineteenth century our knowledge of cancer was largely founded upon morbid anatomy and histology, but it was nevertheless sufficient to provide a rationale for treatment either through the complete extirpation of tumour cells by surgical methods, or later through their destruction *in situ* by radiation. Each of these methods has its recognized limitations, and whether or not they have nearly been reached, there would clearly be immense advantages—since dissemination is an outstanding feature of the disease—in any less local and more systemic control of malignant growth, such as could presumably be achieved by chemical means alone. This has, of course, been recognized from the earliest beginnings of the study of cancer, and we are perhaps inclined to forget that ventures in chemotherapy (of a kind) long antedate the modern developments of surgery. Thus at different times in the past fifteen hundred years there have been applied such diverse agents as belladonna, aconite, mercury, antimony and arsenic, with numerous others in addition. As with many similar examples in the history of medicine, the inefficacy of treatment was reflected in the development of vogues and fashions, of which a good

OCCUPATIONAL CANCER OF THE BLADDER

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return to a job within his mental capacity, is to implant the ureters into the colon (Ward, 1936). Theoretically, this offers the possibility of rehabilitating the patient, should he be able to adjust to a cloacal life, which successful cases are found to do more readily than might be imagined.

So far we have not had a single case of successful recovery after total cystectomy, even in the hands of very experienced

urologists, death in some cases being due to various untoward events, as e.g., paralytic ileus, pulmonary embolus.

Total cystectomy requires the choice of the exactly suitable case. Thus age, general condition, degree of adiposity, are all very important matters in so severe a procedure. In the occupational cases, the appropriate conditions may be more frequently found, as the patient is more likely to be younger, in better general condition, and less adipose than a non-occupational case.

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example is found in the eighteenth-century use of the Vienna hemlock by Storck¹ (*Essay on the medicinal nature of hemlock*, Edinburgh, 1762)

It is evident that a great number of these chemical applications acted—when indeed they had an action—merely as caustics or escharotics, and this applied particularly to the local use of concentrated acids (both mineral and vegetable), of concentrated alkalis, and of various metals and metalloids such as silver nitrate, copper salts, salts of antimony and mercury, zinc chloride, arsenic and litharge. Yet it is possible that one of these agents, if only one—namely, arsenic—had an action which, if certainly not specific, was conceivably less indifferent. It is certainly true that the effects of arsenic in cancer have been studied more continuously than any of the host of substances which has been examined in the past, finding mention from antiquity to the Renaissance in Celsus, Scribonius, Theodoric (? arsenious acid), Fallopius and many others (see also Ronnow, *Mem Acad roy Sci*, Stockholm, 1778). Later we find repeated mention of the powder of Fuscus (a mixture of arsenic, snake-root and soot), of the *pâte arsenicale* of the French surgeons (containing arsenious acid and similar to the *pulvis anticarcinomatosa* of Cosmo), of Dupuytren's powder consisting of arsenious acid with calomel, and of Plunkett's nostrum of white arsenic in crowsfoot, dogfennel and sulphur. Not greatly more than a hundred years ago, Astley Cooper was still employing an arsenical application in the local treatment of certain cases of chimney-sweep's cancer, and a mucilage of arsenious acid was being used by William Marsden, the founder of the Royal Cancer Hospital in 1851. Interest in the therapeutic effects of arsenic was greatly stimulated in 1865, when Lissauer described marked symptomatic improvement following administration of potassium arsenite (Fowler's solution) in leukaemia. A few years later, Billroth published the records of a case of lymphoblastoma which showed repeated and dramatic responses to the administration of Fowler's solution, as a result of which extensive tumour-masses and enlarged lymph-nodes almost entirely disappeared.

However, as indeed we should expect, the therapeutic effect of most of these substances seems to have been illusory, unproved, trivial, or at the most, fleeting, and the best expression of such opinions is seen in the words of contemporary authors themselves. Thus Pott, discussing the advantages of surgery, wrote

"If we were possessed of any medicine, either external or internal, which had been known now and then to have dissolved scirrhus, it would always be right to recommend the trial of them previous to an operation, and it would always be right to defer operating until such trial had been made. But the truth is, we know no such medicine."

and again,

"We are not yet so happy as to be possessed of any medicine which will cure a cancerous habit. When the constitution is thoroughly infected, neither our knives or

caustics will avail, they can only remove the local mischief but can have no effect on the general one in the constitution."

Burrows (*A new practical essay on cancers*, London, 1767), concluded

"that whatever has been proposed for the curing of cancers are merely palliative medicines, and that no real specific has been hitherto discovered for that fatal disorder, although the physicians of all nations, from the time of Hippocrates to the present, have, by numberless researches and experiments, made trial of every thing in nature, from the most innocent drug, to the most virulent poison, both in the mineral and vegetable kingdoms, yet the disease still baffles the power of physic."

Even more forthright was Peyrilhe, also writing in the latter part of the eighteenth century (*Dissertation academique sur le cancer*, Paris, 1776) when he postulated that every attempt to cure a cancer, by any method which is to restore the diseased tissues to a healthy state, is not only vain but absurd. It must freely be admitted we have even better reasons now, than Peyrilhe had then, in support of such scepticism. What are these reasons? In the first place, the fact that the cancer cell is but a modification of the normal somatic cell holds out little prospect of a *chemotherapia specifica* in Ehrlich's sense, whereby chemical substances which, on the one hand, are taken up by certain parasites and are able to kill them, are, on the other hand, tolerated well by the organism itself, or at any rate without too great damage.² Further, the conversion of a normal into a malignant cell is possibly brought about, as we have seen, by a re-orientation of enzyme constitution of such a kind as would not necessarily involve any great change in gross protein-structure or in immunological specificity.

It is considerations such as these which underly the apparently complete absence of any protective reaction on the part of the host against its own tumour, and which militate against any chemotherapeutic discrimination between the normal cell and its malignant variety. Even if Claude Bernard's dictum is no longer strictly accurate, that "tous les medicaments sont, en definitive, des poisons" (*Leçons de pathologie experimentale*, p. 72), it has always been a matter for legitimate doubt whether a therapeutic agent could impair the growth of malignant cells, without equally damaging the normal cells and especially those which are engaged in active division, for example, in the intestinal mucosa, the bone-marrow, and the generative organs. An even more serious obstacle is the fact that the malignant variant is to all intents and purposes quite permanent and irreversible. Hence, even if its growth is impeded by any agent save the most specific (so far unknown), it is likely, after a longer or shorter interval, to recover and recur. In a previous paper (Haddow, 1947)³ we have shown that cancer is no ordinary disease, but rather the unique development of a new and specific cell-type in response to unfavourable conditions, this again is one of the inherent difficulties besetting any attempt at chemotherapy, namely, that we are in effect expected to undo what can almost be regarded as a natural process, which proceeds in one direction with facility, but must from its essence be considerably more difficult to reverse.

Not surprisingly from what we know of such matters the sovereign if rather elusive specificity of this plant appeared to reside only in the true Vienna hemlock (*In Anagallis nullam fuisse veram cicutam*) and Sir John Hill (*Plain and useful directions for those who are afflicted with cancers &c &c with an account of the Vienna Femlock with which Dr Storck has cured many cancers and which is now raised in England* London n.d. [c. 1773]) accordingly went so far as to propagate and distribute this variety in England having obtained the seeds from Storck through Sir John Pringle. After a lengthy test he was however led to conclude that a perfect cure—whether it ever will or will not be found remains in the womb of time.

² [See *BMB* 1946 4, 241]

³ [*BMB* 964]

In the writer's opinion the best prospects of success, and certainly the most satisfying intellectually, should come from persistent investigation of the mode of action of carcinogens, so that by increasingly exact and quantitative knowledge of the process as it occurs in one direction, we may estimate at any rate the feasibility of its deliberate reversal. While this may seem a counsel of perfection, the indications are that the problem is very likely just soluble, even although success must depend upon a very considerable extension of our present knowledge, particularly in the direction of a comparative assessment of the specific growth requirements of normal and malignant cells. If, however, such a solution were to be looked upon as an unattainable ideal—and it is true that we do not yet know any chemical substance capable of producing permanent regression—it is entirely possible that useful therapeutic effects may be brought about by substances powerful enough to inhibit the mechanism of cell division in tumours (directly or indirectly), without affecting the normal tissues unduly. It is perhaps a measure of progress that while we knew of no such substances even a few years ago, we now have three examples—in the treatment of cancer of the prostate with oestrogens, in the action of chloroethylamines in certain cases of Hodgkin's disease and other lymphadenopathies, and in the effects of urethane upon the immature cells in leukaemia. Admittedly, all these examples have very manifest imperfections as practical measures, since none of the drugs is curative and their effects are usually temporary. There is, however, no doubt of at any rate their theoretical importance, as showing that the cancer cell is more susceptible to specific interference than was thought to be possible less than ten years ago.

2. SYNTHETIC OESTROGENS

a. Effects of Castration in Cancer of the Prostate

The recent developments affecting the treatment of cancer of the prostate are mainly due to Huggins and his collaborators at the University of Chicago (treatment by castration and by the administration of oestrogenic substances), to Herrold (1941) at the University of Illinois (treatment with oestrogens), and to Munger (1941) (auxiliary treatment by x-irradiation of the testes) (see Haddow, 1943). While treatment by orchidectomy strictly speaking has no place in a discussion of chemotherapy, its effects on the malignant prostate are so similar to those produced by oestrogens, and the two methods of treatment are so closely connected both in their development and mechanism, that it is impossible to dissociate them completely. Dependence of the prostate gland upon the activity of the testis was recognized by John Hunter, who was aware that the prostate in castrates becomes small and inactive, and the same subject occupied the attention of Bland-Sutton over fifty years ago. Much more recently, Kearns (1941) has recorded prompt retrogression of the normal prostate in two men subjected to castration, one case being of special interest, since the early atrophy was succeeded by regeneration of the gland after an autoplasmic testicular graft had resumed its function. In 1893, White, having observed the retrogression of uterine fibromas after ovariectomy⁴, described the effect of castration on

prostatic hypertrophy, and shortly afterwards several clinicians (e.g. Haydon, Lilienthal, Piercy, White, 1895, Cabot, 1896) published reports describing relief of the symptoms of prostatism brought about by bilateral orchidectomy. Through a number of causes (partly the alleged deleterious general effects of castration and partly the rise of prostatectomy), the procedure fell into disuse, and only Young (1936) appears to have employed it in prostatic cancer, although his experience was limited to two cases with negative result.

Following preliminary studies of the effects of castration on the normal and on the hyperplastic prostate glands of dogs, and on benign hypertrophy of the prostate in man (Huggins & Clark, 1940, Huggins & Stevens, 1940), Huggins and his co-workers (Huggins, Scott & Hodges, 1941, Huggins, Stevens & Hodges, 1941) reported evidence of tumour regression, with other clinical and pathological changes, in cases of advanced prostatic cancer treated by bilateral orchidectomy. In a series of 45 consecutive cases, castration caused no improvement in 5, in 9 cases there was only temporary improvement, and in 31 there occurred a sustained inhibition of the disease, lasting at least as long as 30 months. In the less satisfactory cases a phenomenon of interest was seen on 5 occasions, in a decrease in size of the primary tumour, coincident with rapid extension by metastasis. In those patients who were improved, clinical evidence consisted of decrease in size of the primary tumour on rectal palpation and at cystoscopic examination, stabilization or regression of bone metastases, a decrease in the size of palpable lymph-nodes which were the seat of metastases, improvement in erythrocyte and haemoglobin values, with increased appetite, progressive gain in weight, and diminution of pain. Very similar results were described by Sullivan, Gutman & Gutman (1942) in the following year.

In these cases, pain due to skeletal metastases was wholly or greatly relieved within a period varying between two days and a few weeks, increased calcification occurred at the site of metastases, gain in weight was frequently marked, and frequency of micturition, nocturia and dysuria were partially or completely relieved in most cases, usually within a few weeks. These changes were accompanied by an improved sense of well-being, and several patients who before operation were confined to bed became ambulatory, and others resumed restricted activity. Supporting evidence, substantially confirming such results as the above, was soon brought forward by Neuwanger & Vermooten (1942), Higgins & Gosse (1942), Lane (1943), Smith & MacLean (1943), Burns & Kittredge (1943), Marquardt (1944), and Rathbun (1944), among others. Following a series of reports between 1942 and 1944, Huggins has now more recently (1946) summarized his results after five years. Remissions of varying length occurred in 18 of 20 cases of disseminated prostate-cancer treated by orchidectomy; of these, 5 were alive after 5 years—4 being free from any clinical or laboratory evidence of the disease and one having only slowly-advancing lesions.

b Influence of Oestrogens upon Cancer of the Prostate

In 1941, Herrold reported the results obtained in 12 cases of carcinoma of the prostate which he had treated with diethylstilboestrol. A consistent finding was the relief of pain, often occurring promptly on the institution of therapy.

⁴ Carl Ludwig noted in humans that loss of the ovaries not only stops the menstrual cycles but may also cause a shrinkage of the uterus, and with this observation may be compared the studies of Sir George Beatson (1896) on the atrophy in mammary carcinoma following ovariectomy.

When the first case in which stilboestrol was administered had received approximately 350 mg. over a period of 5½ months, the primary tumour had regressed to half its former size, and was softer in consistency. In other cases there was apparently either stabilization or recession of the carcinomas, accompanied by improvement in general physical condition and in some instances by a gain in body-weight.

In 1940, Kahle & Maltry had reported the treatment of 14 cases of prostatic hypertrophy by means of diethylstilboestrol, combined in 7 cases with various drainage operations. In all these cases there was a marked improvement in, or complete relief of, the symptoms associated with obstruction and the presence of residual urine. As treatment progressed, changes in the size and consistency of the gland were observed in all cases. The findings suggested a trial of stilboestrol in carcinoma of the prostate, and while these authors were discussing this project it was found that one of the cases of hyperplasia also showed adenocarcinoma (at biopsy), and that the malignant cells gave evidence suggestive of regression, presumably as a result of the oestrogen therapy employed in the treatment of the hyperplasia. In 1942, Kahle, Ogden & Getzoff presented 7 cases of carcinoma of the prostate—6 proved by biopsy—which had been treated over two years with diethylstilboestrol. In all the cases, therapy brought about prompt relief of pain and urinary symptoms, the clinical improvement being accompanied by regression of the malignant lesions both primary and metastatic. In Kearns' (1941) series of 37 cases of carcinoma of the prostate, 12 were treated with stilboestrol only, 9 received ethinyl oestradiol only, and 16 received both substances. He described the remarkable clinical amelioration, with gain in weight, relief of pain, improvement in blood-picture, slowing of sedimentation-rate, an approach to normal in the phosphatase estimations, retardation of growth in the skeletal metastases, with diminution in size and reduction of the nodularity and fixation of the prostate itself. As in the use of castration, independent and largely confirmatory results were soon provided by a large number of authors, including Marquardt & Flaherty (1942), Clarke & Viets (1943), Duncan (1943), Heckel (1944), Fergusson (1944, 1946), Fergusson & Pagel (1945), Herbst (1945) and Deming (1946), while many other papers dealt with orchidectomy and oestrogen therapy as well (e.g. Chute & Willets, 1942, Haines & Miceli, 1943, Herger & Sauer, 1943, Ibarra Loring & Marchant, 1943, Graves & Cross, 1944, Nesbit, Pazzos & Cummings, 1944).

In an independent investigation of the influence of synthetic oestrogens upon advanced cancer in man, in which the first case commenced treatment on 18 February 1941, and which was originally prompted by the slight but significant inhibitory effect of various triphenylethylene oestrogens upon animal tumours (Badger, Elson, Haddow, Hewett & Robinson, 1942), Haddow, Watkinson & Paterson (1944) early encountered a case of prostatic cancer in which the presenting symptoms were frequency of micturition, shortness of breath and fleeting chest-pain. X-ray examination suggested the presence of multiple secondary deposits in the bony pelvis, and in the following weeks similar deposits were recorded in the whole of the dorsal spine, in the ribs, femora and humeri, and in the lungs. Cystoscopy showed enlargement of both lobes of the prostate, with a large papillomatous mass in the left wall of the bladder. While biopsy at first gave no undoubted evidence of malignancy, a second specimen showed

a densely cellular mass of columnar-cell adenocarcinoma of prostatic type. Treatment with the synthetic oestrogen triphenylchloroethylene was started on 9 June 1941, and soon produced side-effects (bilateral mastitis and oedema of the ankles) attributable to oestrogen action. During treatment there also occurred a decrease in the frequency of micturition and some betterment of the general condition, which after 8 months was regarded as considerably improved. There was, however, no unequivocal radiographic evidence of change in the skeletal deposits, as judged by comparison, after repeated examination, of the various regions involved, but the prostate itself was described as "not obviously enlarged" after 13 months, when a total of 1,346 g of triphenylchloroethylene had been administered. The case was later treated with stilboestrol in place of triphenylchloroethylene, and is also included as case 6 in a paper by Watkinson, Delory, King & Haddow (1944). It is almost certainly the first case of cancer of the prostate to be treated in Britain with a synthetic oestrogen, and is probably one of the most satisfactory, since the patient is alive and well, with the disease in apparent complete arrest, nearly six years later. This case, with a few others treated with triphenylchloroethylene, raises the question whether any advantage may attach to the use of an oestrogen with relatively-prolonged action, although no substantial evidence is available, the matter is one which should, if possible, receive some further attention. Relatively disappointing results were, however, obtained by Greene (1946) and by the writer and his colleagues (unpublished), in clinical trials of the triphenylethylene derivative known as DBE (*pp'*-diethoxy-triphenylbromomethylene).

Cancer of the prostate is remarkable in that it is histologically discernible in from 9% to 17% of men over 50 years (Rich, 1935, Moore, 1935). Since a good proportion of these are not detected in ordinary circumstances, it is clear that many such cases remain entirely quiescent. Individual cases of the manifest disease are also encountered in which the survival-period is exceptionally protracted even in the absence of treatment, and exceptional caution must therefore be exercised in any estimate of the effects of treatment in this respect. Oestrogen therapy has, however, now been employed for a period sufficiently long at any rate to yield preliminary data: thus Fergusson (1946) has recently compared 27 cases treated between 1940-43 without the use of oestrogens, and 23 treated with oestrogens in 1942-46, with results which indicate, so far as they go, longer survival in a higher proportion. Much larger numbers and closer statistical analysis will, however, clearly be required before any more accurate estimate is possible. No evidence exists that carcinoma of the prostate can be cured by the use of oestrogens, but there is equally little doubt that under this form of therapy the foci of the disease may become quiescent, that life can be prolonged, and that temporary rehabilitation can be achieved.

c. Histological Alterations Due to the Administration of Oestrogens

Herrold (1941) quoted a case (treated by Dunn) which received 480 mg of stilboestrol in 96 days, and in which biopsy of the testes showed a generalized degenerative process with no sign of normal cell-growth and with complete

disappearance of spermatids. The intertubular spaces appeared to be oedematous and to contain a reduced number of interstitial cells.

In their earlier investigations of the influence of oestrogens on prostatic hypertrophy, Kahle *et al* (1942a, b) included a histological study of biopsy specimens obtained after treatment. These showed deviations (from the typical picture of hyperplasia) manifested by a reduction in the number of papillary infoldings, a reduction in the height of the epithelium, decrease in the size of the acini, and stratification of the epithelium with or without vacuolation. The cytological changes in these authors' cases of prostatic carcinoma (similarly treated with stilboestrol) were made the subject of a separate paper by Schenken, Burns & Kahle (1942). Most of the neoplastic cells of each of the cases showed marked nuclear and cytoplasmic regressive changes. The nuclear alterations consisted of reduction in size, progressive condensation of the chromatin, loss of nucleoli, disappearance of mitotic figures, and pyknosis. The early cytoplasmic changes consisted of the appearance of vacuoles, usually located at the base of the cell. As the vacuoles enlarged, the nuclei became displaced towards the lumen of the acinus. This was followed by rupture of the cell-membranes and coalescence of the vacuoles of contiguous cells. Such changes resulted in the nuclei either lying free, or becoming clustered in the centre of the acinar spaces, attached to delicate thread-like remnants of the cell borders. Another note by Schenken & Burns (1942) recorded that identical changes were observed in the metastatic tumour-cells of an inguinal node. Also, Heckel & Kretschmer (1942) described a case in which, at the end of 223 days, when 1,546 mg of stilboestrol had been administered, prostate biopsy showed widespread alteration in the neoplastic cells, characterized mainly by hydropic degeneration and vacuolation. More recently, Fergusson & Pagel (1945) have successfully correlated the clinical and biological findings with the histological progress of the disease as judged by serial biopsy, the cytological changes being a reduction in the number of tumour cells, pyknosis, and concentration of nuclear chromatin.

d Mode of Action of Oestrogens upon Cancer of the Prostate

Huggins *et al* (Huggins, Scott & Hodges, 1941, Huggins, Stevens & Hodges, 1941) pointed out that the action of oestrogens in cancer of the prostate is susceptible of several explanations, any or all of which may be operative. These mechanisms include a direct action on prostatic epithelium, inactivation of androgens, depression of the gonadotrophic agents of the anterior pituitary, and depression of activity of the interstitial cells of the testis. Kahle and his co-workers (Kahle & Maltry, 1940, Kahle, Ogden & Getzoff, 1942a, b, Schenken, Burns & Kahle, 1942) suggested that the rapid change in the consistency and size of the hyperplastic prostate, and in the consistency of the carcinomatous gland—a change sometimes observed as early as 48 hours—argued in favour of a direct, or possibly even selective, action on the epithelial cells. But they agreed that other possibilities, not excluded by a hypothesis of direct action, are firstly, an effect mediated by the anterior lobe of the pituitary on the androgens, elaborated by the interstitial cells of the testis, and secondly, androgen inactivation by a change in the androgen-oestrogen balance. There is little doubt of the validity of Huggins'

general hypothesis of the androgen dependence of prostatic epithelium both normal and malignant, and the remarkable effects of oestrogens in cancer of the prostate would appear to be due to an action upon such residual physiological properties still possessed by the malignant cells.

e Ovariectomy and Oestrogens in Cancer of the Breast

Although the clinical usefulness of castration and oestrogens in cancer is practically confined to carcinoma of the prostate, the fact that their action is not entirely specific to this organ is proved by equally remarkable if much less frequent effects in cancer of other sites, and particularly of the breast. Reference has already been made to the early observations of Sir George Beatson on the palliative effect of ovariectomy in breast cancer, and there has of recent years been a natural revival of interest in this subject. Thus, on the experimental side, the effects of ovariectomy and adrenalectomy on lactation in the mammary tumours of dogs have been studied by Huggins & Moulder (1944), castration for advanced malignant lesions in man has been dealt with by Howes (1944) and by Orndoff (1944), bilateral ovariectomy with a radical operation for cancer of the breast is described by Horsley (1944), the effects of ovariectomy on primary and metastatic cancer of the breast by Treves, Abels, Woodard & Farrow (1944), and the regression of bone metastases from breast cancer after ovarian sterilization by Ritvo & Peterson (1944), while Leucutia (1946) has discussed the value of orchidectomy in the treatment of carcinoma of the male breast.

In the paper by Haddow *et al* (1944) already mentioned, the results are given in 73 cases of advanced cancer which received treatment with the synthetic oestrogens, triphenylchloroethylene, triphenylmethylethylene or stilboestrol. Of 22 cases of late malignant disease of the breast treated with triphenylchloroethylene, 10 showed a significant although temporary retardation, or even partial regression, of the growth of the tumour, but the initial effect of treatment in these cases passed off comparatively rapidly, the ultimate course of the disease was in no way altered, and no evidence was obtained to suggest that treatment could prevent the development of metastases. Of 30 similarly-treated cases of advanced malignant disease other than cancer of the breast, only two (carcinoma of the bladder, carcinoma of the prostate) showed undoubted partial regression of the tumour. Of 14 cases of carcinoma of the breast treated with stilboestrol (by intramuscular injection or by mouth over a period of several months), 5 showed alterations in the growth and behaviour of the tumour similar in nature to those produced by triphenylchloroethylene. Similar cases have been reported by other authors (Tudor Edwards, 1943, Binnie, 1944). If it is true that we have here no real contribution to effective therapy, it is equally true that such responses are of the very greatest theoretical and fundamental importance. Even if the property of oestrogens on which they depend is among the most complex of all drug actions, it is somewhat disappointing that so little progress has been made in deciding the basis of these effects. It is, of course, likely that such relatively massive doses of oestrogens depress the pituitary and hence the ovary, but it is specially important to decide whether the temporary nature of the tumour response is due to an endocrine adaptation to such depression, or to an acquired resistance on the part of the tumour tells themselves.

3 THE β -CHLOROETHYLAMINES

From research on chemical warfare conducted during the war of 1914-18 and in later years, it was early appreciated that exposure to mustard gas (*bis* (β -chloroethyl) sulphide) was capable of producing systemic effects on the haemopoietic and especially the leucopoietic tissues, and on the gastro-intestinal tract (see Gilman & Philips, 1946). As a result of the enormous expansion of such work in the recent war, both in Britain and in the United States, greatly increased attention has been paid to this and other biological effects, and is reflected in a growing literature on the reaction of mustard gas, for instance, with proteins (Kinsey & Grant, 1946, Banks, Bournsnel, Francis, Hopwood & Wormall, 1946), with carboxyl groups and with the amino groups of amino acids and peptides (Moore, Stein & Fruton, 1946), and with methionine (Stein & Moore, 1946) and other amino acids (Bournsnel, Francis & Wormall, 1946), while numerous additional papers deal with other aspects of the chemical reactions of mustard gas and related compounds (e.g. by Stein, Fruton, Moore, Bergmann, Stahmann and others). The wartime biochemical research upon mustard gas which was conducted by the Oxford school has recently been summarized by Peters (1947) and the medical aspects of mustard-gas poisoning by Cullumbine (1947).

Among the many new compounds prepared for the purposes of chemical warfare, special interest attached to the *bis*- and *tris* (β -chloroethyl) amines, as nitrogen analogues of mustard gas, or so-called "nitrogen mustards", and it was soon recognized that these, like mustard gas itself, were not merely contact-vesicants but could induce cytotoxic effects in a wide variety of tissues, and especially in those which are in a state of active proliferation.

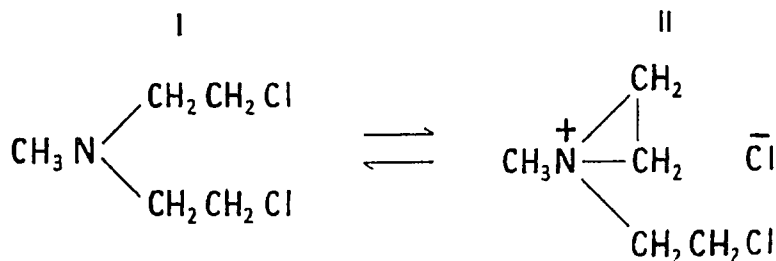
a Cytotoxic and Nucleotoxic Effects of the Chloroethylamines

For both sulphur and nitrogen-mustards, this relatively specific cytotoxic action upon growing tissues is an outstanding pharmacological property, and after adequate doses affects the bone-marrow in the production of leucopenia, thrombocytopenia and anaemia, the intestinal tract in the production of diarrhoea and vomiting, and lymphoid tissues generally in the appearance of persistent lymphatic atrophy. In attempts to ascertain the cytological basis of such effects, it has become clear that the mitotic activity of a variety of cells from unicellular, invertebrate, amphibian, mammalian and plant forms is highly sensitive to inhibition by mustard gas and the chloroethylamines (Gilman & Philips, 1946). Thus, exposure of yeast-cultures to mustard gas can produce an immediate reduction in growth-rate which persists through several generations without recovery, the early cleavage of the sea-urchin egg is inhibited by immersion of either the unfertilized egg or the early zygote in minimally effective concentrations, the exposure of young salamander larvae leads to immediate cessation of growth, attributable to an inhibition of mitotic activity in the proliferating regions, the corneal epithelium of mammals can be depleted of mitotic figures for several days, and mitotic activity is decreased in the lymphoid, myeloid and erythroid series in the rat, as also in the regenerating liver-cells following partial hepatectomy (see also Marshak, 1946). In a recent study, Bodenstein exposed embryos of *Amblystoma punctatum* for 45 minutes to a 0.001% solution of methyl *bis*- (β -chloroethyl) amine hydrochloride: the substance selectively attacked the centres of proliferation, and left the differentiating regions

quite unaffected, so that all mitotic activity was abolished within two days. These toxic effects of the mustards upon cell-division appear to be divisible into two types. First, a mere arrest of mitosis in the resting-stage, brought about by mild exposure, and, second, an extensive nuclear fragmentation (e.g. in the cells of the corneal epithelium) following exposure to concentrations higher than those which involve only a mitotic inhibition. A remarkable example of this latter effect is seen in the pollen grains of *Tradescantia* following exposure to mustard gas (Koller, unpublished), mild exposure prolonged the resting-period but also caused chromosome breaks, while more severe exposure induced multiple breaks with fragmentation, pycnosis and ultimate death of the cell. Further evidence of nucleotoxic action has been obtained through the disturbances produced by the mustards in the structure and function of chromosomes in *Drosophila melanogaster* (Auerbach & Robson, 1946). Following exposure of adult males to doses which did not reduce fertility unduly, genetic analysis of the X chromosomes revealed an incidence of sex-linked lethals greatly in excess of the natural rate of mutation. Mustard-gas mutations have also been described in *Neurospora* by Horowitz, Houlahan, Hungate & Wright (1946). The fact that few if any other chemical agents have such an action on the chromosomal mechanism gives added point to the comparison of the effects of these substances on other grounds as well (particularly the damage to haemopoietic and other growing tissues) with those of α - and ultraviolet radiation.

b Possible Modes of Action of the Chloroethyl Amines and Sulphides

The ability of halogenated alkylamines to form cyclic onium cations had been known for some years, and it was soon established that the nitrogen- and sulphur-mustards owe many of their characteristic properties to an intramolecular cyclization of this kind, which is illustrated in I and II for the case of methyl-*bis*(β -chloroethyl)amine (Hanby & Rydon, in press, Hanby, Hartley, Powell & Rydon, in press, and other references quoted by Gilman & Philips, 1946).



Numerous other references, both published and unpublished, are cited by Gilman & Philips (1946), who also draw attention to the capacity of ethylenesulphonium or imonium compounds to alkylate such functional groups as various amino, imino, imidazole, sulphydryl, sulphide and phenolic groups of amino acids and peptides, inorganic phosphate, glycerophosphate and hexose phosphates, the amino groups of adenosine and thiamine, the pyridino-N of nicotinic acid amide and pyridoxine, and the carboxyl and amino groups of numerous proteins. While it appears generally accepted that the cytotoxic effects of the chloroethylamines may depend upon a similar reaction with some essential con-

stituent, no further discrimination has as yet been possible. In recent papers, Gjessing & Chanutin (1946) and Chanutin & Gjessing (1946) show that the nitrogen mustards are capable of reacting with amino acids, peptides, proteins, purines, pyrimidines, and inorganic and organic phosphates, and that they decrease the viscosity of thymus nucleate solutions, this depolymerizing effect being attributed to the ethylenimine ring transformation-product.

In a recent pharmacological study of the chloroethylamines, Boyland (1946) suggests that their high toxicity may in part be due to the fact that they are lipid soluble substances of low molecular weight which probably penetrate cells readily, and having penetrated are less easily removed on account of combination with essential cell-constituents or the formation of toxic ionized imonium salts. Distinguishing the toxic effects of these substances as vesication, haemoconcentration, diarrhoea, inhibition of mitosis and an acute convulsive effect, Boyland regarded the vesicant action as certainly due to the parent amines and the convulsant action to the reaction-products with water.

In an extension of work on the well known capacity of mustard gas to interfere with the process of carcinogenesis, Berenblum, Kendall & Orr (1936) showed, over ten years ago, that the addition of mustard gas to minced tumour-tissue *in vitro* resulted in reduction of oxygen-consumption and a marked depression of aerobic and anaerobic glycolysis, and Gilman & Philips (1946) quote many examples, arising from wartime research, of a similar action upon such normal tissues as skin, brain, cornea, bone-marrow, spleen, thymus, liver and kidney. These findings led in turn to the possibility that the cytotoxic action of the mustards might be attributable to the specific inactivation of cellular enzymes. In a long list of enzyme-systems of which the sensitivity has been determined, the majority proved either resistant or to be only moderately inhibited, but among the most highly sensitive systems are hexokinase, creatine and pyruvate phosphokinase, inorganic pyrophosphatase, adenylic acid deaminase, and cholinesterase (see Thompson, 1947). With the general hypothesis that the effects of the nitrogen vesicants may be linked with enzyme inactivation, should be compared a specific suggestion that primary inactivation occurs only in the special class of the phosphokinases, which are concerned with phosphate transfer to or from adenylic compounds (see Dixon & Needham, 1946). As, however, in so many other cases, it would appear that certain of the characteristic biological changes (e.g. interference with mitosis) may be produced by concentrations of the chemical agent lower than those necessary to affect either respiration or glycolysis.

c Experimental and Clinical Applications in Chemotherapy
Gilman & Philips (1946), with their collaborators, L. S. Goodman, G. E. Lindskog & S. Dougherty, were the first to investigate the effects of a nitrogen mustard (*tris*(chloroethyl)amine) in malignant disease in man, and were followed by Goodman, Wintrobe, Dameshek, Goodman, Gilman & McLennan (1946) and by Jacobson, Spurr, Barron, Smith, Lushbaugh & Dick (1946). The last authors obtained encouraging results in Hodgkin's disease mainly, failure being encountered in acute leukaemia and multiple myeloma and the results in the majority of cases of myelogenous leukaemia being unsatisfactory. Later Spurr, Jacobson, Smith & Barron (1947) recorded symptomatic control in several cases of Hodgkin's disease out of 29 which were observed over periods ranging from 3 months to 3 years. 94% of 120 courses of treatment resulted in significant

remissions. Nine cases of chronic lymphatic leukaemia showed remissions of between 2 and 24 months, but 5 of the cases had died after 18 months. Remissions were also observed in 4 of 6 cases of lymphosarcoma, and in 7 cases of *polycythaemia rubra vera*, but there was no relief even of symptoms in acute leukaemia, and only transitory effects in chronic myeloid leukaemia. In a recent review of the use of the nitrogen mustards in the treatment of neoplastic disease, Rhoads (1946) draws attention to the similarity of their effects to those of x rays, and cautions that they are in no sense curative for any type of cancer so far studied and that the tumour regressions induced are only temporary, and rarely persist more than several months.

Interesting experimental observations on the effects of the nitrogen mustards on tumour-tissues have recently been published by Karnofsky, Burchenal, Ormsbee, Cornman & Rhoads (1947). The compounds examined were *tris*(chloroethyl)amine[HN3], methyl-*bis*(chloroethyl)amine[HN2], ethyl-*bis*(chloroethyl)amine[HN1] and isopropyl-*bis*(chloroethyl)amine, and were both studied in normal animals and assayed for inhibitory activity against the growth of various types of neoplastic tissue under different conditions (leukaemia in mice, mouse-sarcoma 180, the same tumour growing on the chorio-allantoic membrane of the developing chick-egg, and other tumours in roller-tube culture). All compounds were tested against several leukaemias in mice, by means of an interesting and unusual technique. The given dose having been dissolved in saline and injected intravenously into the leukaemic animal, the latter was killed one hour later, or examined at death when this occurred under one hour with higher doses, when the spleen was removed, and a spleen *Brei* was inoculated into four young mice of the homologous pure line. In such experiments, large doses usually proved either completely cytotoxic to leukaemia cells, or so affected them that their subsequent development in the bioassay might be much prolonged.

As well as providing a measure of the cytotoxic activity of such compounds, this method also illustrates their therapeutic limitation, since the cytotoxic doses of HN3 and HN2 were respectively 7-22 and 8-12 times the LD₅₀ with the ethyl and isopropyl analogues, no clear evidence of cytotoxic activity could be obtained even at much higher multiples. Among other results of interest, it was observed that a dose of HN3 not lethal to a 12-day egg bearing actively-growing sarcoma 180 on the chorioallantoic membrane, within 30 minutes rendered the tumour incapable of growth on subsequent transplantation into mice. In tissue-culture experiments, evidence was obtained of wide differences in susceptibility as between one tumour-type and another, the tumour cells in some cases appearing more sensitive than the normal. In other cases it was seen that tumour cells might be rendered non-viable (as judged by bioassay) while showing no obvious signs of morphological damage.

4 THE ACTION OF URETHANE IN LEUKAEMIA

a Effects of Urethanes upon Animal Tumours

Some years ago, the writer embarked upon an investigation, with W. A. Sexton (Haddow & Sexton, 1946), of the action upon animal tumours of a series of phenylurethanes. This investigation was prompted first by a statement by Lefèvre (1939) that phenylurethane (III) produces mitotic effects exactly similar to those described for colchicine, and secondly by the work of Templeman & Sexton (1945) on the effect of arylcarbamic esters and related compounds upon cereals and

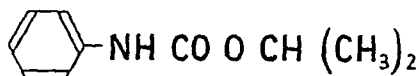
other plant species. These authors paid special attention to isopropyl phenylcarbamate (IV), regarded its effect on nuclear division as probably similar to that of colchicine and, in view of the low concentrations necessary to arrest growth, suggested its use in the eradication of graminaceous weeds.

III



ethyl phenylcarbamate ("phenylurethane")

IV



isopropyl phenylcarbamate

In the first experiments, administration of phenylurethane was soon found to produce mitotic poisoning in the crypts of Lieberkühn in the mouse intestine, but as far as could be judged this effect was not due to retardation of the mitotic cycle at any single phase, and was therefore readily distinguishable from the characteristic effect produced in the same tissues by colchicine. Secondly, phenylurethane (and also isopropyl phenylcarbamate) was found to cause a significant retardation of the growth of spontaneous mammary cancer in the mouse, an effect which persisted only during administration, and passed off rapidly when the drug was withdrawn. Thirdly, both these substances produced a similar retardation in the growth of the Walker rat carcinoma 256. Very surprisingly, it was next found that these effects are also produced by ethylcarbamate (urethane) itself ($\text{NH}_2\text{COOCH}_2\text{CH}_3$), the inhibitory activity of this substance being actually greater than that of either of the phenylcarbamates when tested against the Walker carcinoma. This action of urethane was then found to be accompanied by a profound modification in the histological structure of the tumour, the characteristic cellular structure giving place to a more fibrous structure with an abundant stroma, and indicating a change in the direction of increased differentiation.

b. Clinical Effects upon Leukaemia in Man

Although these effects upon growth were in no way dramatic, the fact that they might be brought about by a known substance as simple and as readily available as urethane, suggested a trial of its action in inoperable cancer in the human subject. Clinical trials, using urethane and isopropyl phenylcarbamate, were therefore started in 1943, first at the Royal Cancer Hospital, London, and afterwards in collaboration with the Christie Hospital and Holt Radium Institute, Manchester. The results of these early trials, mainly in carcinoma of the breast and a miscellaneous group including other types of malignant disease, were mainly negative, apart from possible slight and temporary alleviation in a very few cases. It was, however, decided to pursue the investigation for a further period, and in that part conducted at the Christie Hospital, it was next observed, by Dr Edith Paterson, that urethane produced a fall in the leucocyte-count in some of these cases, following which the clinical

trial was extended to include examples of leukaemia and other lymphadenopathies. From the results, which were later described by Paterson, ApThomas, Haddow & Watkinson (1946), it soon became obvious that urethane does, in fact, produce remarkable changes in leukaemia, represented in the most favourable cases by a fall in total leucocyte-count to normal limits, a tendency for the differential count to approach a more normal pattern, diminution in the size of the spleen and enlarged lymph-nodes, and a rise in haemoglobin level. There is a striking similarity between the leucocyte responses and those brought about by x-ray therapy. There is, however, no indication that permanent benefit may result from the use of urethane in either myeloid or lymphatic leukaemia, since relapses take place, immature cells may reappear in the blood, and all these changes are essentially reversible.

These investigations show one curious feature, namely, that while the effects of urethane on growth were first observed in animal material, and while it was these findings which justified and led to the study of urethane in cancer in man, the characteristic effects in leukaemia were then detected solely as the result of clinical observation. Although the emphasis is now once again on animal experiment, with the objective of determining the mode of action of the drug, it has become clear to the writer that various leukaemias in the mouse and rat are relatively refractory to the influence of urethane, and that the remarkable effect which is shown so clearly in the human, might readily have eluded discovery if attention had been confined to animal material alone. In other cases, positive effects of different kinds obtained with animal tumours have been not at all reproducible in the human, and we have here an illustration of the way in which success in such work is subject to a severe hazard in the variability of response of different tumours.

c. Possible Modes of Action

The results of other experiments have indicated that the growth-inhibitory action of urethanes upon the Walker rat carcinoma is restricted to a few such substances, and is certainly not shown by the great majority of a long series of related compounds. This probable high degree of specificity of the action of urethane obviously raises interesting problems as to its mode of action. Although a great deal of work has been recorded on the suppressive action of urethane, phenylurethane and related carbamates on other growth processes, as in bacteria, protozoa, sea-urchin eggs, plant tissues, and animal tissues growing *in vitro*, little of this is of direct assistance in suggesting the mechanism by which urethane produces its effects in leukaemia.

It might, however, be expected that assistance could be obtained from the extensive literature dealing with urethanes and narcosis. As long ago as 1910, Warburg recorded that if phenylurethane (c. 1/2,000 N) is added to seawater containing eggs of the sea-urchin, *Strongylocentrotus lividus*, cell-division and nuclear division are suppressed, while the oxygen-consumption is only very slightly reduced. Later, Warburg (1921) advanced the general theory that narcosis is due to adsorption of the narcotic in unimolecular layers on the catalytic surfaces involved in oxidation. The next interpretation, an attempt to relate both narcosis and inhibition of cell-division with a general inhibition of dehydrogenases, is faced with the difficulty that the concentrations required to induce narcosis, and to suppress growth,

are often far smaller than those required to inhibit enzyme-reactions Keilin & Hartree (1939) found that urethane and other narcotics, which in the presence of biological reducing-systems inhibit the reduction of the cytochrome components a , a_2 and c , inhibit, on the contrary, the oxidation of b , and they suggested that the effect of urethane consists in bringing about the formation of a not easily dissociable complex composed of dehydrogenase, substrate and cytochrome b , and so making it inaccessible to the portion of the system reacting with oxygen Quastel (1943) also put forward the qualified view that the inhibition of respiration of brain tissue obtained by low concentrations of narcotics under aerobic conditions is due, not to competition of the narcotic with substrates for their dehydrogenases, but to the affinity of the narcotic to a special component playing an important part in the complete respiratory process of the cell—the narcotic effect being restricted at low concentrations to a tissue component which is possibly a flavoprotein. It is of special interest here that the “activity system” of Fisher & Stern (1942) (that is, that portion of the over-all respiration which is most sensitive to inhibition) appears to be associated with the maintenance of normal mitosis, for when it is differentially suppressed by appropriate concentrations of urethane, abnormal nuclear figures appear In a special case, Johnson, Eyring, Steblay, Chaplin, Huber & Gherardi (1945), have summarized our present knowledge of the relation between luminescent oxidation, the respiratory pathway in bacteria, and the inhibitory action of urethane the luminescent system shows a characteristic sensitivity to urethane and is affected to a much greater extent than total oxygen-consumption.

When the first results on animal tumours were being considered, it was suggested by Professor A. R. Todd that urethane might conceivably act by competing with some natural amine involved in the biosynthesis of nucleotides. The possibility that urethane might act by inducing a deviation especially, say, in purine synthesis, became even more suggestive when its action upon leukaemia was discovered, in view of the long-recognized aberration of purine metabolism in leukaemia, and speculations regarding a relationship between leukaemia and uratisis in subjects carrying a latent tendency to gout. Investigations of the purine metabolism in several of the cases reported by Paterson *et al* (1946) have not as yet been sufficient to yield any useful data, largely because in none of them was the uric-acid content of the blood unduly raised before treatment It is, however, remarkable that colchicine, which was earliest employed for its action upon gout, then observed to produce effects upon the bone-marrow (Dixon & Malden, 1908), later discovered to have its profound influence on mitosis, and since known to have some action in leukaemia (Kneidler, 1945), should be imitated by arsenic both in the treatment of leukaemia (see Forkner, 1938) and in effects on the mitotic cycle (Piton, 1929, Chodkowski, 1937, Dustin, 1938), and now to some extent by urethane in leukaemia and on cell-division.

It is an important problem whether the primary action of urethane is upon the growth mechanism or upon differentiation-processes—to the extent that the two are separable At the present moment one regards the latter as the more likely, and can only suggest that the drug may act on growth primarily through the processes of maturation, and in leukaemia by tending to remedy some deficiency in these processes Quite apart from any question of its practical clinical usefulness—and this, as has been shown, is clearly limited—there is little doubt of the value of the observation itself for the future study of errors of differentiation in general

5 CONCLUSION

From the evidence summarized in this and a previous paper (Haddow, 1947),* there can be no misunderstanding as to the almost insuperable problem which the chemotherapy of cancer presents, and which, in search of a comparison, we can almost liken to a biological counterpart of the squaring of the circle It is indeed true that those who have considered the matter most thoroughly are under the least illusion as to its practicability That the subject will continue to be investigated, quite regardless of success, is, however, equally true, and it must therefore be our duty to stimulate this process as far as possible, while at the same time never failing to underline its inherent and therefore inescapable difficulties The slight advances of the past few years are, however, more than were accomplished in any previous period, and it is surprisingly likely—and very much to be hoped for—that a review such as the present will comparatively soon be out of date Exactly one hundred years ago W H Walshe, then the professor of pathological anatomy in University College, wrote as follows (*The nature and treatment of cancer*, 1846)

* There is no medicine known having claims to the character of a *specific* in cancerous diseases, nor even endowed with the special attribute of invariably modifying the course of the affection But this is no reason that such a medicine may not be found the history of mercury and quinine teaches the folly of absolute scepticism in respect of the reality of specific agents The efforts of those, who are placed in a position fitted for the purpose, should be unceasing in the search after such a medicine, for nothing can be more unphilosophical than to conclude that it does not exist because it has not yet been found It is manifestly not from the *οι-ολλοι* of drug-lauders that the discovery of so inestimable a boon is legitimately to be expected it is from him who, thoroughly versed in the diagnosis of disease has enough of incredulity in his intellectual composition to doubt the evidence which is not repeated time after time in similar cases, who has a fund of patience which no labour can exhaust, and a conviction of the grandeur of his task, which disappointment, be it repeated ever so often, can never succeed in shaking”

It is to be feared that the problem is more unpromising than even Walshe believed, but on his note of buoyancy—which will certainly be needed for a long time to come—we may end

* [BYB 964]

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SURVEY OF THE DANAKHIL DESERT

G Jannone, G Ferro-Luzzi & L Mara. *Risultati di una spedizione tecnico scientifica nella Danakalia Settentrionale. Es eruo* [Asmara] 1946 (Monografia No 2 del Bal'etuna della Società Italiana di Medicina e Igiene Tropicale. Sezione Eritrea)

This book comprises a detailed and informative account, sent by Major J L Congdon Controller of Agriculture, and Lieut-Colonel C B R Pollock, Principal Medical Officer, to the British Military Administration at Eritrea, of an expedition to the Danakhal Desert undertaken by members of the Agricultural and Medical Departments. The report is divided into 4 parts. The first is concerned with the physical geography of the district and the social conditions of the inhabitants written by Dr Luigi Mara, who is a malarologist and is responsible for Part III, which deals more particularly with malarial problems and the prevailing genera and species of *Culicines*. Part II, by Professor Jannone, an agrarian entomologist, treats of agricultural and pastoral activities forestry such as it is, mining and the locust troubles. In Part IV Professor Ferro-Luzzi writes of nutritional problems.

The expedition travelled 1,216 kilometres and extended over a period of 30 days. The area of what is known as Eritrean Dankalia is approximately 25,000 km.² and extends from 12° 22' to 15° 30' N latitude and 39° 45' to 42° 10' E. longitude, and has a population of just under 20 000, mostly living in the northern parts and the coastal villages. The area includes the Dankalia or Danakhal Depression to the west (a term which might be fitly applied to the effect produced as well as to the physiography, for judging from the photographs of the country it consists largely of barren, stony ground with scanty tufts of bush-growth). To the east of this lies the hilly district. The average rainfall along the coastal belt is 186 mm. at Massaua in the north, 104.2 at Thiù, about the middle, and 27.1 at Assab in the south. The temperature is lowest in January, 25.9° C at Massaua, 25.1° at Assab, highest in July, 35.2° and 35.3° respectively, and the mean for the year, 30.2° and 29.9° C.

Except at Badda on the west and, to a less extent, Saraita on the east, no irrigation is carried out, but a certain amount of grain is grown. Large wadis might be utilized elsewhere for increasing grain production, but are not. The people in the interior are engaged in rearing goats and some sheep, cattle, donkeys, mules and camels, but, except in the more hilly districts, where the rainfall is greater, the pasture land is poor. The need for food necessitates frequent movement and a nomadic life.

From the leaves of the Dum Palm (*Hyphaene dankaliensis*), an alcoholic drink, duma, is made, and the leaves are used also for making baskets, mats, ropes, etc. The date palm (*Phoenix dactylifera*) also grows there. Locusts (*Schistocerca gregaria*), common in parts of Eritrea, the eastern lowlands, for example, do not abound in Dankalia, the barrenness of the land and the low rainfall may account for this, but many dead locusts are seen in the salt-lake district to the west. It is thought that swarms pass over this and are killed by poisonous gases exuding from thermomineral holes in the ground. In the Zarga district to the south-east of Badda sulphur works, and at Dallol a little further south of Badda, potassium compounds known as *carallite* and *silvine* are obtained and used as fertilizers.

Dr Mara, in his account of the malariology of the area, shows that this disease is not a very serious problem because, owing to the dry climate, there are only two, comparatively small, areas where the moisture favours mosquito-breeding. The Buri peninsula to the north is near the malarious eastern lowlands of Eritrea, and the common vector is *A. gambiae*. At Assab, in the south, near the Arabian coast, is an endemic centre, here the vector is *A. culicifacies*, the local variety being *adenensis*. Six other species of *Anopheles* exist, but only one, *A. funestus*, seems to play the part of transmitter. *Aedes* species are also found, among them *Aedes aegypti* and domestic breeding-sites are fairly plentiful among the urban population on the Red Sea or eastern side.

Part IV is very instructive. It deals with food and nutrition the different food customs of the coastal the plain and the hill peoples their nutritional balance or imbalance, and indications of malnutrition and deficiency diseases. The diet habits of the nomads of the hills and the plains differ from each other and from those of the coastal zone. The two former live almost entirely on the milk of their goats. Those living in the lowlands have in addition meat in small amount and dura (sorghum) this as a whole contains less fat and vitamins and is of a little lower calorie value than the other which has a high vitamin content and biological value and a calorie value of 2 600. Those living on the coast, having no pasture exist on a diet comprising milk, meat, fish and cereals, together with the Dum-palm fruit already mentioned, and some 'duma'—the alcoholic drink made from the palm. The diet as a whole, though more mixed is in many respects inferior to either of the others and contains less protein, less fat less vitamin, but more carbohydrate and has a calorie value of only just over 2 000. Even though the best of these is below the European standard for health, no signs of malnutrition or of any of the avitaminoses are seen in the highland people, those in the lowlands are living on the margin of a breakdown and their resistance to disease must be weak. Among the coast-dwellers a few cases of avitaminosis-A and -B were observed, showing that the borderline of safety had in some already been overstepped, but even in these the symptoms were not very severe, hyperkeratosis of the skin (avitaminosis-A) and glossitis (-B) being the most marked.

The book contains several well-reproduced photographs and good line-maps. The expedition must have had a strenuous time to have accomplished so much in the short period of 30 days.

H Harold Scott

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DANISH TEXTBOOK ON VENEREAL DISEASE

S Lomholt. *Venerereal diseases in general practice*. Munksgaard Copenhagen Lewis, London. 1946. 25s.

This work is a translation, in easy idiomatic English of the author's Danish text-book, which reached its 3rd edition in 1945. It is introduced to English-speaking readers in a laudatory foreword by Dr A. C. Roxburgh. In his own preface the author explains that he had already prepared the English version of his book and it had been printed when the German occupation of Denmark in 1940 closed all communications between that country and England. Instead of re-arranging the book to incorporate in it the important new matter which has accrued during the war years and since, the author has thought it suitable to deal with this in a supplement occupying 19 pages at the end. English-speaking readers to whom this work comes for the first time may well think that the author would have been better advised to wait until the position in regard to penicillin had become a little more stable and his own knowledge of the newer methods had been tempered by longer experience of them.

Over half the book is devoted to syphilis, which is well illustrated with 12 coloured plates containing 29 figures and with 59 figures in black-and-white. This section is by far the best in the book though not every syphilologist will agree that haemorrhagic encephalopathy starts within a few hours of an injection or with the author's rather summary dismissal of sulpharsphenamine, or that solusalsarsan is more reliable than sulpharsphenamine. In the causes of non-specific Wassermann reaction the author has not included recent vaccination a typical pneumonia and some other conditions which recent work has

stigmatized as possible sources of error. In treatment, the two schemes recommended by the League of Nations Committee are described, the author preferring the "Plan of Intermittent Treatment". With one similar to this he says that in 152 previously untreated cases he has obtained freedom from relapse in all during a period of 2 to 5 years and complete sero-negativity in 143.

Chancroid is dealt with in about 6 pages, illustrated with 6 figures (3 in colour). Not everyone will agree with the author's recommendation to incise a complicating bubo, and sulphonamide treatment should not be dismissed in 2 lines.

In 10 pages are described phagedena, lymphogranuloma inguinale (well illustrated with a colour plate), granuloma venereum, ulcus insons puellarum or ulcus vulvae acutum, balanoposthitis, phimosis, paraphimosis, herpes genitalis, condylomata acuminata, molluscum contagiosum, and crab-louse. This section is illustrated with 7 figures in colour and 3 in black-and-white.

Gonorrhoea is dealt with in the remaining 66 pages of the main body of the book. Although it contains much useful information, it also contains much with which British venereologists would not agree. Thus we long ago abandoned the use of strong silver preparations in the treatment of gonorrhoea in either males or females, and palpation of the prostate during acute stages is considered likely to favour the development of epididymitis. It would not be agreed that irrigation is difficult for patients to practise on themselves. The author advises that the urethra should not be irrigated with a disinfectant prior to the passage of an instrument. He says that this applies particularly to potassium permanganate, in an old case of urethritis, in which there is usually an infection with mixed organisms, most British venereologists would not use potassium permanganate in any case, because it is useless in such infections, but they would certainly use an antiseptic such as mercury oxycyanide as a precaution against the instrument forcing the organisms deeper into the tissues.

In laboratory diagnosis of gonorrhoea, two small points seem to require revision. Under the technique of gram-staining, it is said that methyl violet deteriorates with age, this is directly contrary to what is said in Mackie & McCartney's *Handbook of practical bacteriology*. On the other hand nothing is said of the deterioration, with age, of Lugol's iodine solution, which is certainly very important. In the account of the gonococcal complement-fixation reaction, it is stated that in the haemolytic system the amboceptor "is inactivated serum of rabbits treated with injections of an extract of guinea-pig kidney". The reason for using this instead of the usual suspension of blood cells is not stated.

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MEDICAL MYCOLOGY

J. E. Mackinnon. *Zimologia medica*. Imprinta. El Siglo Ilustrado, Montevideo, 1946.

This work on medical mycology is the result of studies carried out by the author at the Montevideo Institute of Experimental Hygiene. His interest in the subject was first aroused by his having studied with Professor Talice and afterwards with Professor Langeron, and work on the Monilias formed the basis for his doctorate thesis. Reading this present work impresses upon one how erroneous has been the incrimination of many species as pathogenic, mere fortuitous association having been declared, after inadequate investigation, to be aetiological connected with disease. The author considers the following Genera *Candida*, *Trichosporon*, *Torulopsis*, *Pityrosporon*, *Rhodotorula*, *Endomyces*, *Saccharomyces*, *Endomycopsis* and a few others briefly. He describes their morphology, macroscopic and microscopic, the question of three phases of their growth, the smooth, mycelial, the rough, bacterial or spore phase, and the mucoid, and their transmissibility of one to another. Also their biology, adding a few words on their reputed or possible pathogenicity and the results of experimental tests on rabbits, rats and mice.

After a few introductory remarks on classification and technique of growth and culture, each of the above Genera is considered in turn. Sixteen species of *Candida* are thus described, but the

majority are not pathogenic. *C. albicans* is found in the alimentary canal in the debilitated, as in thrush. Experimentally, intravenous injection of blastospores gives rise to small abscesses in all organs in 5-7 days, these he calls "seeding abscesses" (lesions de siembra), later there may be infarct lesions or "lesions of elimination" and "lesions of secondary infection", in which the *C. albicans* secondarily invades, e.g. a liver abscess or some pulmonary condition. It may form small nodules and undergo calcification or caseation. Another species, *A. tropicalis*, is found in cases of so-called broncho-moniliasis and paronychia in the tropics, but its pathogenicity is doubtful.

Four species of *Trichosporon* are described, one of which, *T. beigelii*, is pathogenic, causing White Piedra, it is found also in nodosities of Black Piedra, but probably in this case as a parasite of the *Piedra hortae*, the actual cause of the black variety. Nine species of *Torulopsis* follow, *T. neoformans* is probably the only one pathogenic, causing *Torulosis*, or European blastomycosis. *Pityrosporon* is thought by some authors to be the cause of pityriasis, others, however, regard it merely as a secondary invader. Of *Rhodotorula*, 9 species are described, but those as yet studied have not been proved to be pathogenic.

Much of the work described seems to have been confirmatory of that already published and the references to the literature are numerous. No details of any cases are presented. There are good illustrations of the naked-eye and the microscopical appearances of the cultivated fungi. From the morphological and biological aspects the book should prove very useful as a work of reference.

H. Harold Scott

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THE GENUS MYCOBACTERIUM

P. Hauduroy. *Inventaire et description des bacilles paratuberculeux*. Masson Paris, 1946. 200 francs.

Professor Hauduroy has catalogued 160 members of the genus *Mycobacterium*, giving the authors' descriptions of the bacteria. These descriptions vary from a mere statement that acid-fast bacilli were observed in certain material to long and detailed accounts of the morphological, cultural, biochemical and serological characters of the bacilli described, together with an account of the pathogenicity of these to various laboratory animals. This catalogue collects, for the first time, a mass of published material, much of which is not easily available. It is, therefore, not only of historical interest, but also of importance to anyone interested in the genus.

It is not clear, however, that Professor Hauduroy does any service to determinative bacteriology by grouping together so heterodox a collection of bacteria under the designation "paratuberculous". It is true that all the bacteria described are members of the genus *Mycobacterium* but, except for that, the relationship of many of them to *Mycobacterium tuberculosis* seems very remote. There seems little justification for calling *M. M. smegmatis*, *phlei*, *stercusis*, *butyricum* and many others "paratuberculous". He excludes from the paratubercle bacilli only the classical tubercle bacilli, the leprosy bacillus and John's bacillus. If the word "paratuberculous" is to be used at all, and there seems little justification for it, it should surely be confined to those strains of acid-fast bacilli which have been isolated from tuberculous lesions, but which do not conform to the accepted characteristics of the classical tubercle bacilli. The saprophytic acid-fast bacilli, so many of which are described here, have no connexion with tuberculosis. It would have been less controversial and nearer to reality if the monograph had been somewhat expanded and entitled "A Catalogue and Description of the Genus *Mycobacterium*".

The chapters on pathogenicity and tuberculin production are of great interest. They raise matters of fundamental importance in the understanding of the genus. What factor determines the pathogenicity of any member of the genus? The answer is not here, but it may be that the stimulus will be provided to find an answer.

The description of the vole bacillus on pp. 111 and 112 is misleading. The pathogenicity for laboratory animals given here is not that described by Griffith.

984

RADIOLOGY

E. A. Zimmer. *Die Durchleuchtungstechnik der Thoraxorgane*. Schwabe, Basel 1946. 12 Sw francs.

This small volume is printed in German on good quality paper and illustrated with first class diagrammatic reproductions which emphasize the essential features seen on the screen and in the radiographic appearances of the more common lesions within the thorax.

The text is concise yet no essentials are missed, and it is arranged with great care to exclude the rare, but to include all the lesions usually met with at a chest-clinic. The instructions and explanations of technique are sound and complete.

The routine conduct of the examinations necessary to examine the upper abdomen, diaphragm, lower lung fields, middle fields and hilus, upper fields and apices, the heart and main vessels, oesophagus and mediastinum, and to demonstrate the lesions and their characteristic appearances, are clearly defined. Few small books so well achieve what the author set out to do. He is to be congratulated on producing such an excellent and instructive account of the uses of fluoroscopy. All who wish to know how to conduct screen examinations of the chest cannot do better than learn the contents of this book.

James F Brailsford

* * *

985

P. van Pée. *Précis de radio-diagnostic*. Masson, Paris, 1944. 700 francs.

This is a very sound précis of diagnostic radiology which any student who wishes to acquire the rudiments of the art and has a knowledge of the French language would do well to assimilate. The volume explains the physics of x radiation concisely but distinctly. It then sets out the technique for the examination of each system, the skeletal including neurological, gastro-intestinal, gall bladder, cardio-vascular, respiratory and genito-urinary. In each of these the radiographic features of the more common lesions are described and illustrated with the assistance of good radiographs or outline drawings.

The author is to be congratulated in the selection of material he has used and the way he has put it together. The volume is printed on excellent paper with clear type which, in these days, are all too scarce with English volumes.

James F Brailsford

986

THE KIDNEY IN PREGNANCY

H. Pigeaud & H. Dumont. *Les néphropathies gravidiques*. Masson, Paris 1946. 140 francs.

This book is another addition to the already extensive literature dealing with the group of diseases now known in Britain as 'toxæmias of late pregnancy' or 'albuminuria of pregnancy'. The authors recognize in their first chapter the difficulties of terminology and observe that, although albuminuria is a cardinal symptom, the renal lesion is a secondary one. They deal with the chief symptoms and signs—albuminuria, oedema, and hypertension—and discuss in detail the theories of the etiology of the rise in blood pressure. They believe that metabolites play some part in the causation of this, without placing the blame on any one substance. Discussing possible endocrine factors, they believe that a general endocrine imbalance may play an important part. They conclude that renal ischaemia due to vascular spasm is responsible for the main symptoms and signs of hypertension, and that this is caused indirectly by endocrine imbalance.

This book is a comprehensive treatise on a difficult subject which, although it brings one little nearer an explanation of the true origin of a mysterious disease, brings many fresh ideas and restates the problem with admirable clarity.

The authors have obviously not had access to the most recent literature on the subject from Britain and the United States. It is to be hoped that a new edition may incorporate some of the new facts that have arisen from research into a problem which remains one of the most difficult and therefore one of the most fascinating in obstetrics.

987

PERIPHERAL NERVES

E. Villiger. *Die periphere Innervation*. 10 Aufl. Schwabe Basel 1946. 16 Sw francs.

The popularity of Emil Villiger's book *Die periphere Innervation*, edited and revised by Eugen Ludwig, is sufficiently indicated by the fact that it has now reached its tenth edition.

The text deals with the peripheral nervous system mainly from the point of view of its gross anatomy, but there is also a short section on the functional aspects of peripheral nervous lesions, illustrated by photographs of clinical cases. The topographical anatomy is well presented, and there are some excellent illustrations which help to explain the text, while in the brief clinical section the subject matter is presented in an appealing manner.

For the British reader however, the book tends to be somewhat unbalanced. The preclinical student will find the descriptive anatomy unnecessarily detailed, and there is no description of the microscopic anatomy of the peripheral nervous system—a subject in which many recent advances have been made. On the other hand, while the topographical descriptions are adequate for the advanced student, the functional and clinical aspects of the subject are insufficiently emphasized. Further, the absence of any references to the literature renders the book of limited value.

The author has not set out to produce a work of reference and bearing this in mind, it may be said that, though the book covers a restricted field, systematists will find it of definite value.

G. Weddell

988

"LEWIS'S"

Lewis's 1844-1944. A brief account of a century's work. Lewis London 1945. Free on application.

In 1844, Henry King Lewis, then a young book-trade apprentice of 22, purchased a small bookselling and stationery business in Gower Street, London. From that small beginning has grown the modern Lewis's familiar to thousands of medical students, with its publishing, its bookselling and its circulating-library activities.

This well produced booklet has been issued to commemorate the centenary of the firm, and to show its close connexion with the medical profession. When and why the founder of the firm decided to specialize in medical and scientific bookselling and publishing is not clear, for the earliest works he published were of a distinctly religious character. The close proximity of University College and University College Hospital were probably important factors in the transition. Similarly, the dissatisfaction of medical readers with library facilities gave Mr Lewis the idea of setting up a circulating library of medical and scientific books. This was in 1853, and to-day the catalogue of that library includes some 24,000 titles of books of importance.

Throughout its long history, the firm has maintained friendly and intimate relations with the medical profession. The author of this centenary history has dipped into the firm's archives to give us unusual glimpses of medical authors, of Sir Thomas Barlow as a young student fearfully returning a library volume he had damaged, and of the loss, fortunately unique in the history of the Firm, of a statistical table for a monograph of Sir William Osler's.

Perhaps the spirit of Lewis's may best be summed up in the words of the present chairman, Mr H. L. Jackson, in his preface, "Even if books may have been replaced by the micro-film, things of the mind will still be of prime importance, and if 'Lewis's' should be in existence in that distant time, may it still be helping in the distribution of knowledge."

H.A.J.

989

ANGLO-AMERICAN MEDICAL PROGRESS

A. Abaza. *Acquis médicaux récentes dans les pays alliés*. Doin, Paris, 1946.

The purpose of this book is to provide, for members of the medical profession in those countries that were isolated during the years of enemy occupation, an account of the advances in the medical treatment in Britain and in the USA since 1940. This purpose has been most competently fulfilled by Dr Abaza, who

is a member of the medical staff of UNRRA, and his book will be found useful in countries other than those for whom it was especially intended. The subjects reviewed include penicillin, the sulphonamides, atypical pneumonia, DDT, oestrogens, new forms of insulin, fluorescence, microscopy, anouracil and ligation of the ductus arteriosus. A large list of references is given in each case.

990

CLASSICS OF SCIENCE AND MEDICINE

Under the above title, Messrs Davis & Orioli, of 56 Maddox Street, London, W 1, have published a remarkable catalogue (No 125) of early scientific and medical books. The catalogue contains 444 items, among which are the first English edition (1597) of Roger Bacon's *The mirror of alchemy*, the first edition (1600) of William Gilbert's *De magnete*, William Harvey's *De generatione animalium* (1651), Robert Hooke's *Micrographia* (1667), the *Fasciculus medicinae* (1500) of Johannes de Ketham, Ambroise Paré's *Dix livres de la chirurgie* (1564), and many other works of exceptional interest.

In his foreword, Mr J I Davis points out that many of the items included have not been offered for sale for many years and, he adds "I fear that neither I nor any other bookseller will be able to get together such a collection in the future." This unique catalogue is amply illustrated with facsimiles, and medical bibliophiles will need no encouragement to justify Mr Davis's hope that it will not be thrown into the wastepaper basket.

991

JOURNALS RECEIVED

The first three numbers (March, June, and September, 1946) of the *British Journal of Pharmacology and Chemotherapy*, have now appeared. This new quarterly periodical, published for the British Pharmacological Society by the British Medical Association, is designed to assemble the work in all fields concerned with the effects of chemical substances on animals and the living tissues, previously scattered throughout numerous periodicals. It will publish original contributions on all branches of pharmacology and experimental chemotherapy, including biochemical and pathological aspects. Provision will also be made for short communications and for brief notes on technique. It is edited by a board consisting of Professor J H Gaddum (Chairman), Dr H R Ing (Secretary), Dr N Mutch, Dr C M Scott, Professor F R Winton, Professor J H Burn, Dr F Hawking and the Editor of the *British Medical Journal*.

Sir Henry Dale explains in a foreword to the first number the reasons for the issue of the new periodical. Pharmacology and its vigorous offshoot chemotherapy, he says, have risen rapidly to major rank among the group of scientific disciplines which come within the scope of experimental medicine, and it is impossible for the American periodical, the *Journal of Pharmacology and Experimental Therapeutics*, to cover the important new discoveries and developments from Great Britain and the British Dominions as well as from the United States of America. Sir Henry Dale concludes by expressing the hope that there will still be abundant opportunities of co-operation and friendly interchange between the new British periodical and the *Journal of Pharmacology and Experimental Therapeutics*, which has so long and so well served British as well as American achievements in this field. The contents of Nos 1 and 2 were listed in the *Guide to the Journals* of an earlier number (BMB 961). The contents of No 3 appear in this issue.

* * *

The first number of another new journal to be published by the British Medical Association also appeared in March, 1946. *Thorax* is the journal of "The Association for the Study of Diseases of the Chest" and, like the *British Journal of Pharmacology and Chemotherapy*, is published for a private society by the British Medical Association. It is primarily intended for the publication of original work on diseases of the chest and relevant anatomical and physiological studies. The joint editors are Norman Barrett and J G Scadding of the Brompton Hospital, London, S W 3, and they are assisted by an editorial

committee consisting of W G Barnard, R C Brock, J Gilhes, Clifford Hoyle, A S Johnstone, E W Wayne, and the Editor of the *British Medical Journal*. Like the other new specialist periodicals now published by the British Medical Association, it will appear quarterly, and the price of the annual subscription is 25/- Its contributions are of a high standard and it is well produced technically. The full contents of the first two numbers of *Thorax* were listed in the *Guide to the Journals* in BMB, 1946, 961. The contents of No 3 appear in this issue.

* * *

We have received two new periodicals from Belgium. *Acta clinica belgica*, to appear six times a year, is the continuation of the *Bulletin de la Société Clinique des Hôpitaux de Bruxelles*, which ceased publication in 1940. The first number is published under the auspices of the Société Clinique, but with the foundation of the Société belge de Médecine interne, it is expected that the new society will assume the responsibility of publication. The *Acta clinica belgica* will publish original articles dealing with clinical medicine in all its aspects, review articles, clinical observations, and analytical reviews of books, monographs and articles both Belgian and foreign.

* * *

The *Revue médicale de Liège*, on the other hand, is intended for the general practitioner. It is the organ of the Association des Anciens Elèves de la Faculté de Médecine de Liège, and will appear at fortnightly intervals. One of its chief objects, the editorial assures us, is to act as an intermediary between the specialist and the young general practitioner who can afford neither the time nor the money for post-graduate study.

* * *

Tuberculosis Index and Abstracts of Current Literature is published by the National Association for the Prevention of Tuberculosis for the Tuberculous Educational Institute. Its object is to provide a complete list of current articles on all aspects of tuberculosis as they appear in world scientific and medical literature. The abstracts are grouped into broad subject headings, and are then arranged alphabetically under the author's name. It is regrettable that the two numbers so far published should bear different titles, and that no mention of volume or individual number appears in either of them.

* * *

Arquivos do Instituto Químico-Biológico do Estado de Minas Gerais. The first volume of this new Brazilian periodical, which is to appear at irregular intervals, has been received. It contains the scientific work of the Instituto Químico-Biológico, the work of which is devoted to the problems of human and animal pathology. The 16 articles contained in this volume cover a wide range of subjects, from antiscorpionic serum to Chagas' disease, and have short abstracts in English.

* * *

Farmacoterapia Actual (Madrid). The first 2 volumes and 3 numbers of the current volume of this monthly journal, now in its third year of publication, have just reached us. Each number contains at least one general review article and 3 or 4 original articles, while brief sections are devoted to recent pharmacological developments, clinical notes, matters of historical interest, and abstracts from foreign journals.

* * *

A number of the *Revue de Laryngologie, Otologie, Rhinologie* has just been received. Enclosed in one number we find 65^e année, septembre 1944, No 1. 66^e année, décembre 1945, No 1. 67^e année, janvier 1946, No. 1, nomenclature which will undoubtedly make it a problem piece for medical bibliographers. Each number, fortunately, is paginated separately, but difficulties of precise dating are increased when we read in the editorial preface to année 65, No 1, septembre 1944 "C'est avec une profonde émotion que je présente à nos lecteurs, en ce novembre 1944 [our italics] le premier numéro de la *Revue de Laryngologie libérée*". Each number consists of original articles followed by clinical observations, while an index bibliographique of the current literature appears in the introductory pages.

Book Reviews

The prices quoted are those which obtain within the United Kingdom. Publications are classified according to the Universal Decimal Classification and the classification number of each publication is given at the right

ANAESTHESIA

992

616-089 5

Modern Anaesthetic Practice

EDITED BY *The L's Sir Humphrey Rolleston & Alan Morrison*
SECOND EDITION LONDON H. K. L. SPOTTISWOODE LTD. 1946
viii + 150 PAGES 7 ILLUSTRATIONS. 22 x 14 cm. 1s. 6d. [£0.63]

Editorial preface. Introduction. (i) Theoretical aspects of anaesthesia and analgesia (ii) the use of volatile anaesthetics (iii) nitrous oxide anaesthesia in surgery (iv) basal narcosis (v) endotracheal anaesthesia (vi) spinal anaesthesia (vii) anaesthesia and analgesia in midwifery (viii) anaesthesia and the child, (ix) anaesthesia in dentistry (x) local anaesthesia and analgesia (xi) post-operative care anaesthetic aspects (xii) risks of explosion in anaesthesia. Index.

The second edition of this excellent little book bears little evidence of the difficulties of war time publishing except for a few errors of spelling. The print is clear and the general literary standard is exceptionally high for a medical text-book. Much of the pleasure and benefit that any anaesthetist will derive from it is attributable to the fact that it is essentially practical and is based, largely, on the personal experience of the individual contributors. It is inevitable that they should disagree on some minor points, notably on the safety of ether in the presence of an open fire (pp 84 and 137) but these conflicts of opinion are surprisingly few.

The book is introduced in a general review written in the superb English one has learned to expect from Dr. Blomfield. The chapter on theory is not of great value and the more important practical points are dealt with elsewhere. Dr. Hewer's wide knowledge and powers of exposition could have been better employed in some other section. The account of nitrous oxide is excellent, but four pages are occupied with a description of its use in major surgery that is inappropriate in a book of this kind. The statement that respiratory complications are reduced after the use of basal hypnotics is debatable, as is the inclusion, among disadvantages, of the necessity for the anaesthetist to examine the patient before an administration. The recommended maximum dose of pentothal—3 g—is rather larger than is generally considered wise and the statement "at the first sign of undue restlessness [after pentothal] an adult patient should receive an intravenous injection of omnopon, 1/3 grain" does not agree with the same contributor's remarks on page 48.

The chapter on endotracheal anaesthesia is one of the best in the book. Yet one must question the advice to lighten anaesthesia before extubation—"foreign material which may have collected in the vicinity of the trachea or nasopharynx can thus be expelled spontaneously by the unaided efforts of the patient himself." The first phase of coughing is the taking of a deep breath, which may carry such foreign material down into the lungs. Surely, "the vicinity of the trachea or nasopharynx" should be cleared by the anaesthetist *before* extubation. It is doubtful, too, whether it is justifiable to obtain practice by passing tubes at the end of long operations.

The section on Anaesthesia and Analgesia in Midwifery is good, if somewhat repetitive, and shows an extensive practical knowledge of the subject. "Owing to the constancy of the mixture the induction of analgesia is rapid" is a *non sequitur*. To the author's call for "some really satisfactory analgesic drug

that will give relief at the early stage of labour" one might offer pethidine, which, surprisingly is not mentioned. Caudal anaesthesia is described in unnecessary detail for a technique that is not recommended to the readers. Anaesthesia and the Child is excellent, but is not atropine, 1/50 1/75 grain, rather much for a child between two and five years of age? Anaesthesia in Dentistry reveals some confusion in the author's mind on the mechanics of rebreathing (page 101). "The readiness with which these growths [carcinoma] bleed often makes the patients unsatisfactory subjects for nasal nitrous oxide, and evipan or pentothal, are satisfactory in these cases"—this is dangerous talk. Local Anaesthesia and Analgesia (why both?) is the least valuable and least up-to-date section of the book. For example, "For such major operations as lobectomy or thoracoplasty, a high spinal anaesthetic is far more suitable [than local or regional nerve block]." Dr. Magill's Post Operative Care. Anaesthetic Aspects is masterly and Dr. Hasler's well balanced account of Risks of Explosion in Anaesthesia makes a worthy tailpiece. The index is adequate.

Criticism of detail must not be allowed to obscure the fact that this is a very good book. It can be recommended with confidence to all occasional anaesthetists and could be read with profit by any.

993

616 672-006 46 613 6

CANCER

Cancer of the Scrotum in Relation to Occupation

S. A. Henry LONDON OXFORD UNIVERSITY PRESS 1946 viii + 112 PAGES 30 ILLUSTRATIONS 22 x 14 cm. 15s. [£0.75]

(i) The nature and site of the disease, (ii) landmarks in the history of cancer of the scrotum, (iii) the results of notification of the disease, (iv) investigation of fatal cases of the disease, (v) the time necessary for the production of the primary growth, (vi) treatment, (vii) preventive measures, (viii) concluding remarks. Bibliography. Index.

Dr. Henry in his preface speaks too unassumingly of this work as a "paper", whereas it is a monograph on a subject on which he has had unique experience, and one which will always be an authoritative work on industrial cancer of the skin. It is based on a Hunterian Lecture given by him at the Royal College of Surgeons in 1941 with the title "Cancer of the scrotum in relation to occupation". But the work under review covers a much wider field, as it records 3,333 cases of epitheliomatous ulceration or cancer of the skin, according to the part of the body in which they occurred in workers in 100 different occupations, these cases came under Dr. Henry's notice whilst he was one of H.M. Medical Inspectors of Factories, or have been reported to him since his retirement from this post.

Dr. Henry began to take a special interest in the subject when he was appointed Secretary to the Home Office Departmental Committee set up in 1925 to investigate the cause of cancer of the scrotum, which in 1910 had been found by S. R. Wilson, of the Manchester Royal Infirmary, to affect men working in the cotton spinning mills on a machine known as a mule. In this capacity, Dr. Henry undertook the laborious work of searching the death registers of Oldham and its hospitals, and those of Manchester and other cotton spinning towns.

He found the first record of scrotal cancer in 1887, 30 years after shale oil had been added to animal oil for lubrication in the mills, and 12 to 15 years after it had become the sole oil used. Knowing of the production of epithelioma of the skin of laboratory mice by the application of mineral oil by A. Leitch in 1922, and of Dr. Henry's own investigations, the Committee reported in 1926 that mulespinners' scrotal cancer was probably caused by mineral oils used for lubricating the spindles of the mule and thrown off by them on to the clothes.

Dr. Henry begins his work with an historical survey from 1775, the year in which Percival Pott described scrotal cancer of chimney sweeps caused by the tar content of soot, of epithelioma of the skin caused by tars and mineral oils. In tracing the history of the disease before Percival Pott's days he quotes Shakespeare's of the disease before Percival Pott's days he quotes Shakespeare's to references in *Cymbeline* and *Love's Labour's Lost* to references in chimney-sweepers, and reproduces two striking illustrations from prints of 1630 and 1638. The long tortuous chimneys, needing small boys to climb inside to clean them, date from the great

fire of London, 1660. Although brushes now replace boys, the incidence of the disease in chimney-sweepers was 754.7 per million in Dr Henry's last returns.

Of the 30 illustrations, the first 12 are excellent reproductions of scrotal cancer in various stages of its growth and of early pre-cancerous or keratotic changes of the skin. The others are of men working in occupations in which they are liable to contract the disease. In 4 tables are given the sites of the disease in 3,333 cases and the relation of the site to occupation, the number of fatal cases in various industries and the incidence per million workers, and an analysis of 1,631 fatal cases in 100 different occupations. By far the most numerous were in occupations involving the use of tar or pitch (1,892 cases of which 429 were sited on the scrotum) and in cotton mule-spinners (1,229 and 793 respectively). Three graphs show the annual distribution of mortality and the time required for the production of malignancy after exposure—a very important point in claims for compensation for disablement.

After the report of the Home Office Committee, the Manchester Cancer Committee in 1926 established a scientific research department at the University, under Dr C. C. Twort, to examine the carcinogenic nature of mineral oils according to their origin. The Committee had the benefit of the advice of Dr Henry, who was one of its members, and samples of oil used in cotton mills were brought by him for investigation. Shale oil was found to be so carcinogenic that its use for lubrication was entirely discontinued. Other mineral oils varied in potency according to their origin, whilst animal and vegetable oils were harmless. Sperm oil added to a mineral oil diminished its danger.

Dr Henry recommends early notification of the appearance in a spinner of any suspicious change in the skin, so that it can be effectively treated and cured by operation, x rays or radium. Cotton spinners are advised by handbills to be examined every few months by a medical man for this purpose, as is done in some mills, but usually such advice is not followed.

To prevent the disease the employment of a non-carcinogenic mineral oil is essential, and the only likely one is a white oil prepared by chemical purification of the less toxic mineral oils. One such oil was shown by Dr Twort to be harmless when it was painted for long periods on the skin of mice, and several firms now market oils of this type, although these have not been tested biologically.

A new appliance that can be fitted to the mules to diminish contact with oil will contribute to safety, as will also an additional pair of short pants worn about the groins under the usual overalls, but spinners are seldom willing to wear such a garment.

The Manchester Committee on Cancer presented a small book on mulespinners' cancer to all medical practitioners in the towns in which cotton is spun. All mill-owners and operatives' officials had copies of it, while 10,000 handbills were distributed amongst the spinners themselves, containing advice similar to that advocated by Dr Henry.

As a medical referee for industrial diseases for 20 years, during which time I have benefited by Dr Henry's advice, I have seen some 200 cases of cancer of the skin or precancerous keratotic changes in spinners. The numbers have been decreasing since the safer oils have been used, but even if the non-carcinogenic white oils alone are handled, epithelioma of the skin will still occur in men who have previously been using mineral oils, for, as Dr Henry's graph shows, it may take from 13 to 40 years to develop after original exposure to mineral oils.

There is a good list of references to authors quoted, with a full and detailed index. It is a book that should be acquired by everyone interested in industrial diseases, not only those of a malignant character, and by every medical and scientific library.

E. M. Brockbank

994

616-0064 615 849

The Results of Radium and X-ray Therapy in Malignant Disease: Being the Second Statistical Report from the Holt Radium Institute, Manchester

COMPILED BY *Ralston Paterson, Margaret Tod & Marion Russell*
EDINBURGH: E. & S. LIVINGSTONE LTD., 1946. 147 PAGES.
ILLUSTRATED 24 x 15 cm. 7s. 6d. [£0.375]

Introduction. Part I (i) General survey (ii) malignant disease—cases referred showing disease classification (iii) malignant disease—all sites grouped

together, (iv) bladder, urinary, (v) breast, (vi) maxillary antrum, (vii) mouth and lip, (viii) pharynx and larynx, (ix) rectum, (x) skin, (xi) uterine body, (xii) uterine cervix, (xiii) other sites. Part II (i) Scientific report with comparative analyses of the various techniques employed, (ii) bladder, urinary, (iii) breast, (iv) larynx, (v) lip, (vi) lymph nodes, cervical, secondary to mouth cancer, (vii) maxillary antrum, (viii) mouth, (ix) parotid gland, (x) penis, (xi) pharynx, (xii) reticulo-endothelial disease, (xiii) skin, (xiv) uterine body, (xv) uterine cervix, (xvi) vulva, (xvii) various sites: anus, bone, nasal cavity, orbit, ovary, soft parts, testis, thyroid, vagina, (xviii) various sites (poor prognosis groups): Hodgkin's disease, lung and mediastinum, lymph nodes (supposed primary), oesophagus, prostate, rectum, (xix) various sites (small groups): brain, middle ear, salivary glands, scrotum, stomach. Part III (i) 10-year report of results of treatment during years 1932 and 1933, (ii) all sites grouped together, (iii) breast, (iv) mouth and lip, (v) skin, (vi) uterine cervix, (vii) conclusion, (viii) relevant publications by members of the staff.

This report is the second of its kind to be published from the Holt Radium Institute, Manchester. The workers at this centre have taken full advantage of their unique opportunity of treating large numbers of cancer cases by radiotherapy, and their observations and results, as embodied in the present report, are probably without equal as a record of positive achievement in cancer treatment.

The report is in three parts, each subserving a different purpose. The first part is a general survey of the treatment of malignant disease, written with a view to providing information for the general practitioner, the hospital administrator, and the intelligent layman. In the second part an attempt is made to evaluate the different methods of radiation treatment and to outline the techniques used. The third and shortest part refers to the first report and gives the 10-year results of the cases treated in 1932-1933.

The general survey forming Part I is admirable in every respect. It points out the essential factors necessary if treatment is to be increasingly successful. The first of these is the education of the patient and private doctor so that early signs and symptoms of cancer can be recognized, and cases can be sent for treatment while the disease is still curable. That cancer is curable requires repeated emphasis, as it is too often still regarded as an incurable malady. Conclusive proof of the value of treatment is furnished by the results obtained, since of 8,298 cases of malignant disease treated by radiotherapy between 1932-1938 inclusive, 86% of the early, and 63% of the early and moderately early cases survived 5 years. The fact that under half of the cases were advanced and gave only a 13% five-year survival-rate is a sad commentary both on the all-too-common failure to recognize the early case and the limitations of treatment.

The second essential mentioned is the need for an organization to make adequate treatment immediately available. The Holt Radium Institute is an outstanding example of a radiotherapy centre soundly organized to deal with cases coming from a large area in North-west England. From 1932-1943 the number of patients seen has risen from 1,313 to 4,530 per annum. The need for the third essential, namely clinical and scientific research, requires no comment.

Part II is a detailed report intended for those engaged in the treatment of cancer and is an attempt to relate radiotherapeutic methods with results and to assess the value of the different methods used. Surgical treatment is considered only where it is combined with radiotherapy.

The authors have set themselves a task which is admittedly difficult but clearly necessary if radiotherapeutic progress is to be maintained. Although they have succeeded up to a point, it is too much to expect that all their statements and conclusions will find general acceptance among radiotherapists. In reading this section of the report one cannot help gaining the impression that a high degree of standardization of technique has been attained at the Holt Radium Institute. Whilst this obviously facilitates treatment where large numbers of patients are concerned, it also means that the need for individualization of treatment may readily be overlooked, and the clinical aspects of radiotherapy may be sacrificed at the altar of organizational efficiency.

Part III gives the 10-year results in tabular form, and it is of interest to note that, in the majority of cases, the patient who survives 5 years eventually dies from some cause other than cancer, the 5-year-survival figure thus providing a satisfactory index of the value of treatment.

It would be difficult to praise this report too highly. It should be read and studied by all interested in, or concerned with the treatment of cancer, and, if possible, imitated by other radiotherapy centres.

M. Lederman

HEALTH

995

A Charter for Health

By a Committee of the British Medical Association under the
Chairmanship of Sir John Boyd Orr LONDON: GEORGE ALLIN &
UNWIN LTD 1946. 95 PAGES ILLUSTRATED 19 x 13 cm. 6s
[£0.3]

The essentials of health (i) the role of medicine (ii) preventable disease
(iv) the family (v) the home (vi) food (vii) occupation (viii) recreation
(ix) mental health (x) health education (xi) some statistics, (xii) the birth
rate (xiii) the doctors' prescription. Index.

Although the contrary is often suggested, statesmen have shown increasingly that they recognize the prerequisites of health to be much more than items within even the best medical services. Medical Officers of Health have for long recognized the physical environment and the right use of material resources as the background to a healthy life and moreover, have stated explicitly the conditions which must be fulfilled in order to ensure health.

"A Charter for Health" is an authoritative, yet non-technical exposition of how "positive health", as it is called, is to be promoted and maintained for the masses. It is, in other words, a popular guide to an aspect of social medicine, comprehensive, as far as it goes, well illustrated self-explanatory, easy to read and balanced, as might be expected from the galaxy of medical stars who have collaborated to produce it.

Diet, housing, family life, work and leisure, childhood and adulthood, mental health and bodily health are each competently reviewed. The chapters dealing with the house as a home and with mental aspects of health are especially clear and vivid. They reveal the minds of writers who know their subjects well enough to make them simple without loss of accuracy. Statistical aspects of health and disease are well presented, too. The treatment would not always satisfy the expert, but that is probably a commendation.

Indeed, the only general criticism which might be advanced of this excellent little book is that, in one sense it is too highly selective. The connexion between health and the prevention of some diseases is made clear, but what is not made clear is that many diseases would be little affected by an improved general environment and a healthy way of living. Though understandable, it is, perhaps, unfortunate that the importance of technical medicine and medical organization is not sufficiently stressed, for to judge by their pronouncements, many statesmen have tended to discount their significance in disease-prevention. The book had to be limited in scope, but limited reference to this aspect of medicine is an omission of consequence. It is offset, however by an insistence on the role of doctors as health advisers to the nation—as health educationists at the political level.

The book meets a need which has not been met by any other work of its size. It should be read especially by everyone interested in current medical thought in England, by those concerned with politics who are without medical knowledge, by practitioners of "Health Education", and by teachers of biological subjects. The ordinary man who wants to know about the principles of health promotion could also study it with profit, and many doctors would be repaid for the time they spent on reading the book, both because it is useful for the practitioner to know how the subject is presented to the general public, and also for the broad perspective of its contents.

F G

GYNAECOLOGY AND OBSTETRICS

996

A Pocket Obstetrics

Arthur C H Bell LONDON: J & A. CHURCHILL LTD 1946
viii + 148 PAGES 13 ILLUSTRATIONS 19 x 12 cm. 7s. 6d. [£0.375]

(i) Anatomy (ii) normal pregnancy labour and puerperium (iii) abnormal pregnancy (iv) abnormal labour (v) abnormal puerperium (vi) obstetric operations, (vii) the baby

As this is a synopsis of obstetrics the style is necessarily staccato. The author takes for granted that the reader already

possesses some knowledge of the subject. Treatment is based for the main part on the practice of Queen Charlotte's Maternity Hospital. The main value of the book is for students who wish to revise rapidly for obstetric examinations.

997

Gynaecological Endocrinology for the Practitioner

P M F Babop EDINBURGH, E & S LIVINGSTONE LTD., 1946
viii + 124 PAGES 19 x 13 cm. 7s. 6d. [£0.375]

Preface (i) The endocrine control and their modes of administration (ii) hormones (v) dysmenorrhoea (vi) the menopause (vii) pregnancy (viii) pregnancy tests (ix) hormone assays Appendix commercial preparations of sex hormones. Index.

This small book is addressed to the general practitioner and contains the conclusions reached by one who has devoted many years to the study and practice of clinical endocrinology. There is probably no clinical subject in which there is a greater need for a balanced outlook and sober judgment. The author has succeeded in presenting to the practitioner a reliable guide to hormone therapy in the female. There is a useful Appendix containing a list of commercial products, with the names of manufacturers and prices.

Any practitioner who treats gynaecological cases should possess this book. The author is to be congratulated on presenting so disordered a subject in such simple, lucid and balanced language.

998

A Practical Handbook of Midwifery and Gynaecology

F T Haultain & C Kennedy THIRD EDITION EDINBURGH, E & S LIVINGSTONE LTD., 1946 x + 383 PAGES 3 PLATES 47 FIGS 23 x 14 cm. £1

(i) Anatomy, development and physiology (ii) diagnosis of pregnancy (iii) antenatal care and calculation of date of confinement (iv) normal labour (v) puerperium (vi) pathology of pregnancy (vii) haemorrhages during pregnancy (viii) abnormal presentations in labour (ix) delayed labour (x) contracted pelvis (xi) other major complications of labour (xii) obstetrical manipulations and operations (xiii) complications of puerperium (xiv) puerperal sepsis (xv) infections of genital tract (xvi) displacements of the uterus (xvii) disorders of menstruation and sexual abnormalities (xviii) diseases of the uterus (xix) diseases of ovary and Fallopian tubes (xx) diseases of the vagina, vulva and urethra (xxi) venereal diseases affecting the generative organs (xxii) sexual disorders (xxiii) therapeutic use of hormones in obstetrics and gynaecology (xxiv) some gynaecological operations (xxv) the infant. Appendix the uses of X ray in obstetrics and gynaecology. Index.

The present edition of this book is published after an interval of 10 years. Much new matter has been included, such as sections on the use of x rays in obstetrics and gynaecology, the use of drugs in labour, the therapeutic use of hormones. There is now a chapter on the infant, written by a paediatrician.

The authors are teachers in Edinburgh University and have presented their subject in a way that makes it easy for a student to grasp and assimilate. The classification is lucid and the sub-sections are enumerated in such a manner that all the salient features catch the eye without the fatigue of having to filter one's way through verbiage. The book is essentially practical and the authors take pains to indicate the reasons for their preference for a particular procedure. It is full of practical hints—for example, the clamping of the umbilical cord at the level of the vulva will show by the position of the forceps whether the exposed portion of the cord has lengthened with the separation of the placenta. The greater part of the book deals with obstetrics, and rightly so, since so much gynaecological illness is a sequel to faulty judgment and technique.

It is a pity that a handbook of this kind still perpetuates descriptions of gynaecological operations. The majority of readers will probably never perform any of these operations, and those who intend to operate will require much more ample instructions in surgical technique.

This book can be strongly recommended to students and those practitioners who wish to revise their obstetric knowledge. The authors have succeeded admirably in fulfilling the task they set themselves.

HUNTERIAN MUSEUM

999

61(074)

The Hunterian Museum: Yesterday and To-morrow

G Grey Turner LONDON CASSELL & CO LTD, 1946 viii + 87
PAGES, 43 ILLUSTRATIONS 22 x 14 cm 15s [£0.75]

Introduction (i) Choice of subject, (ii) museums before Hunter, (iii) how Hunter was inspired, (iv) inception and growth of the collection, (v) Hunter's method of work, (vi) the workroom, (vii) the collection after Hunter's death, (viii) the museum in its hey day, (ix) the disaster and after, (x) the future, (xi) museum technique Conclusion Index

This small volume passes on to a larger audience the Hunterian Oration for 1945. It might well be called, "Yesterday, to-day and to-morrow", for, as one reads Professor Grey Turner's absorbing story, it is evident that the dire misfortune of the Hunterian Museum provides the stimulus and opportunity for a yet more glorious to-morrow—a future in which all the younger members of the profession may, and indeed must, play an active part.

The author begins with a general review of early medical museums, passes on to a sketch of the life of John Hunter and examines the various factors which may have inspired his work. He pays tribute to the many loyal workers who have cared for the collection, interpreted its message, and maintained the Hunter tradition through the long years of development—William Clift, Richard Owen, James Paget, William Pearson, Samuel George Shattock, Arthur Keith, and many others. In the devoted work of such men is to be found the secret of its past success, for no collection in the world could rival it.

But the clouds are gathering and total warfare has no consideration for the treasures man has accumulated, in a day it may end the work of centuries. And so it was, on the night of 10 May 1941, when nearly two-thirds of the contents of the Hunterian Museum were destroyed by blast and fire. Professor Grey Turner tells a moving story of this disaster. Elaborate precautions had been taken to safeguard the collection, but they had failed. The surviving exhibits were removed to dispersal centres out of the danger area and the Museum Committee proceeded to plan for the future.

It was decided that the new museum should be built up round the surviving specimens to illustrate the development, the structure and the functions of man, together with the accidents and diseases to which he may be a victim, with such references to the animal kingdom as may help to elucidate the problems involved. The museum would be less diffuse and its object more clearly defined. The lessons of the past had been learnt, everything must contribute to the two main functions of such a museum—education and research. The last two chapters are rich with valuable suggestions for the organization and administration of the museum, they deal with the vexed question of private collections, with special exhibits and fresh developments, more especially in the anatomical field. There is also a plea for closer co-operation between the medical museums at home and abroad.

Throughout the book the author speaks with the sympathy and authority of one who loves his subject and appreciates the part which such a national museum may play in the future history of medical progress. It is a monograph which all may read with profit for, in the past, few have realized the important part the medical museum has to play in education and research.

S H D

LEPROSY

1000

616-002 73

Leprosy

Sir Leonard Rogers & Ernest Muir BRISTOL JOHN WRIGHT & SONS LTD 1946 xii + 250 PAGES 88 ILLUSTRATIONS 22 x 14 cm 25s [£1.25]

(i) History of leprosy, (ii) the distribution of leprosy, (iii) conditions influencing the prevalence of leprosy, (iv) theories of the causation of leprosy, (v) the communicability of leprosy, (vi) conditions influencing the contagiousness of leprosy, (vii) history, (viii) principles and practice of present-day prophylaxis, (ix) description and distribution of bacillus, (x) the primary infection—incubation—mode of onset, (xi) classification of types of cases, (xii) clinical signs and pathology of the lesions, (xiii) leprosy lesions considered regionally, (xiv) incidence, (xv) diagnosis, (xvi) prognosis, (xvii) historical review, (xviii) lines of treatment recommended. Appendices Index.

The first edition of this book appeared as long ago as 1925, the second in 1940. The early appearance of this third edition is due to the destruction by bombing of a large part of the publisher's remaining stock during the air-attack on Bristol. Many of the blocks of illustrations were also destroyed.

It is indeed fortunate that the authors and publisher have had the enterprise, not only to make good the loss, but also to produce an improved edition with more and better illustrations. Additions have been made to the sections dealing with prophylaxis, etiology, diagnosis, and the clinical aspects of the disease.

Although research work on leprosy has naturally been less during the war, it is interesting to find that some new drugs, such as "diasone" and "promin", are regarded by Dr Muir as being of distinct value in certain forms of the disease. A book on leprosy cannot be expected to be a best-seller, but the earlier chapters of this volume, by Sir Leonard Rogers, will be found intensely interesting, not only by medical men, but also by many laymen whose work lies in countries where leprosy is a problem.

The section dealing with the development of modern methods of control is of exceptional interest because the author was himself the originator and persistent advocate of these methods. It is not too much to say that Sir Leonard has initiated a new epoch in the history of leprosy, he has not only worked out better methods of treatment and prevention, but, thanks to his energy and vision, he has changed the whole outlook on the disease. Hope has been brought to the leper and the way has been shown to the establishment of an organization for the systematic control of the disease. Dr Muir has for many years collaborated with Sir Leonard and has unrivalled knowledge of the clinical aspects of the disease in India and many other parts of the world.

Few medical subjects can have had a stronger combination of expositors, and medical men in tropical countries will long owe a debt of gratitude to the authors for their authoritative guidance in a difficult subject. Even the beginner will find the book easy reading, and the excellent illustrations will be of the greatest help to him. The lines of treatment recommended are stated clearly but without undue dogmatism. Special emphasis is laid on the importance of general treatment as an adjunct to the special methods with which the authors' names are closely associated. No worker, medical or lay, in the field of leprosy can afford to dispense with a careful study of this book.

NUTRITION

1001

612 39

Food and Nutrition: The Physiological Bases of Human Nutrition

E W H Cruickshank EDINBURGH E. & S. LIVINGSTONE LTD 1946 vii + 326 PAGES, 41 ILLUSTRATIONS, 22 x 14 cm 16s [£0.80]

(i) Introductory the evolution of human dietaries (ii) the problem of world malnutrition, (iii) the problem of nutrition in Great Britain (iv) the problem of nutrition in Great Britain 1939-45, (v) the energy requirements of the body, (vi) protein requirements of the body, (vii) foodstuffs and their fuel values, (viii) mineral salts in nutrition, (ix) vitamins and dietary deficiency diseases, (x) Vitamin A and the vitamin B complex, (xi) vitamins and dietary deficiency diseases (cont.), (xii) Vitamin C, D, E and K, (xiii) bread, (xiv) milk, (xv) protein rich foods, (xvi) vegetarianism, (xvii) dietary standards and dietary planning, (xviii) dehydration and preservation of foods, (xix) diet and dental caries, (xx) the appraisal of the nutritional state in individuals and communities, (xxi) the Food and Agriculture World Organization Index.

The reader purchases a book such as this for one of three reasons. A personal knowledge of the author and his work suggests a presentation of the object matter which it would be profitable to possess. The book may form an integral part of the bibliography of this subject. Or, finally, it might be the book which could be handed to a beginner or one moderately acquainted with the subject matter or to an advanced worker in the field to be read with profit.

On receipt of this book, it must be confessed that it was welcomed for the first of the reasons stated, but a careful reading of the text leaves the reviewer in doubt as to the purpose and public the author desired. Whilst the text contains much interesting material, it fails too frequently in clarity and accuracy.

Human nutrition is by no means an exact science, but in a text of this kind surely a greater simplification is permissible in regard to the human requirement for protein than is given in Table 3C, p 44, and pp 70 and 71, and for Vitamin C, Table 3C and

pp 132 and 133, to take only two examples. Apparently, the ingestion of food raises the daily caloric requirements of a 65 kg man from 1,684 (p 58) to 2,400 Calories (p 62).

We read, p 73, 'It has long been known that carbohydrate has a sparing action on protein metabolism. Several investigators have shown that if a man be starved, the output of nitrogen in the urine falls. This indicates that, after the first two days of starvation, when carbohydrate stores have been rapidly diminished, the body obtains energy from protein and fat. When, as in the last stage of severe or prolonged starvation, almost all fat has disappeared, the body has to rely on its protein for the supply of energy. The loss of protein can, however, be stopped if carbohydrate be administered in amounts sufficient to meet the energy requirements of the resting man, i.e. about 35 Calories per kilogram. Whenever the protein wastage stops, the tissues will be restored by a rebuilding of the protein part of their structure. This is the extreme case, and here only carbohydrate, as glucose, is effective.'

Butter is classified as a protein rich foodstuff, p 201. Pasteurization of milk, dehydration of foodstuffs, appraisal of nutritional states in individuals and communities, diet and dental cares and the Food and Agriculture World Organization are among the topics discussed.

The text, which contains more than 50 tables and 41 figures, is set in a bold, clear type on a good paper.

C C N V

PENICILLIN THERAPY

615 779 5

1802

Penicillin: Its Practical Application

Under the General Editorship of Sir Alexander Fleming
LONDON, BUTTERWORTHS & CO. LTD., 1946. x + 360 PAGES
59 ILLUSTRATIONS. 23 x 14 cm. [110s. £1.15]

General (i) history and development of penicillin (ii) chemistry and manufacture of penicillin (iii) pharmacy of penicillin (iv) pharmacology of penicillin (v) bacteriological control of penicillin therapy (vi) methods of administration. Clinical: (vii) prophylactic use of penicillin (viii) generalised infections and gas gangrene (ix) chest infections (x) chest surgery (xi) wounds and fractures (xii) burns and plastic surgery (xiii) orthopaedic surgery (xiv) osteomyelitis (xv) obstetrics and gynaecology (xvi) abdominal infections (xvii) ophthalmology (xviii) venereal diseases (xix) otitis media and otitis externa (xx) otitis media and otitis externa (xxi) dermatology (xxii) dental and oral infections (xxiii) penicillin in animal diseases (xxiv) penicillin and the general practitioner. Index.

1003

Penicillin in General Practice

J. L. Hamilton-Paterson LONDON, STAPLES PRESS LTD., 1946.
95 PAGES. 10 ILLUSTRATIONS. 17 x 11 cm. 5s. [£0.25]

(i) The history of penicillin (ii) the nature and properties of penicillin (iii) the principles of penicillin treatment (iv) methods of administration (v) preparations of penicillin (vi) the treatment of systemic infections with penicillin (vii) the treatment of pulmonary infections (viii) penicillin in some miscellaneous surgical conditions (ix) penicillin in other miscellaneous conditions (x) treatment of infections of the eye (xi) treatment of infections of the ear, nose and throat (xii) treatment of infective conditions of the skin (xiii) penicillin in venereal disease. Appendix. Index.

1004

Practical Points in Penicillin Treatment

G. E. Beaumont & K. N. V. Palmer LONDON, J. & A. CHURCHILL LTD., 1946. vi + 16 PAGES. 1 ILLUSTRATION. 18 x 12 cm. 1s. 6d. [£0.075]

Britain, true to her traditions, has been slow in the publication of books on penicillin, but as the almost simultaneous appearance of these three books shows, this lag is rapidly being overcome. Such tardiness is not without its compensations when dealing with a rapidly developing new therapeutic measure. Varying in their approach to the subject, from the comprehensive-ness of Sir Alexander Fleming's book to the potted synthesis of Dr Beaumont's, they each subserve a useful function.

Pride of place must be given to the volume edited by Sir Alexander Fleming. Practically 20 years have elapsed since the accidental contamination of a culture plate in St. Mary's Hospital gave the first inkling of a development in bacteriology that, as a result of the hazard of war, has developed into the greatest advance in the history of therapeutics. It is only fitting, therefore, that the first book on the subject to be published in this country should appear under the aegis of the original discoverer. For the purpose of his book the editor has collected around him a distinguished team of contributors, all of whom have had considerable experience of the use of penicillin, and all of whom approach the subject from an essentially practical point of view. The editor himself contributes the chapters on the history and development of penicillin and the bacteriological control of penicillin therapy. These two chapters, along with others on the chemistry and manufacture of penicillin, the pharmacy of penicillin (by Professor Berry), the pharmacology of penicillin (by Professor Garrod) and methods of administration, constitute the first section of the book. The second and greater part of the book is devoted to chapters dealing with the use of penicillin in various diseases and systems, covering the whole range of penicillin therapy. There is even a chapter on the use of penicillin in animal diseases. A useful concluding chapter is entitled 'Penicillin and the general practitioner'.

The general standard of the book is high, and most criticism could be countered by the defence that knowledge concerning penicillin is developing so rapidly that any book on the subject is out of date to a certain extent before it is published. Even so, it is to be regretted that some reference at least has not been made to the problem of the therapeutic efficacy of the different penicillins particularly in the treatment of syphilis. Two more serious criticisms are that sufficient emphasis is not laid upon (i) the danger of masking syphilis in the treatment of gonorrhoea with penicillin, and (ii) the danger of mastoiditis developing insidiously and unnoticed in a certain number of cases of otitis media treated with this antibiotic. The standard of the bibliographies provided by different contributors is curiously variable; some chapters having no references at all. A protest must be made against the use of 'neonates' in referring to young infants. More than one distinguished paediatrician would turn in his grave were he to learn that 'sixty-nine neonates were admitted to the Hospital for Sick Children, Great Ormond Street'. But taken all in all, this can safely be described as the most reliable book on the subject that has yet appeared, and it is no exaggeration to add that it is a book that must be read and studied by every practising doctor, whether general practitioner or consultant, physician or surgeon.

Dr Hamilton-Paterson's booklet contains an amazing amount of information and can be safely recommended for the general practitioner who wants to have a book on the subject which he can slip into his pocket and therefore always have by him to consult in the course of his rounds. Much of the information is given in a tentative manner as the opinions of different writers on the subject. A certain amount of dogmatism, combined with more concentration on the commoner conditions encountered in general practice, would have enhanced the value of the book for the general practitioner.

To attempt to epitomize in 16 pages the use of penicillin, as Dr Beaumont and Dr Palmer do, is not without its dangers. A little knowledge can be a dangerous thing, and this leaflet could be recommended only for use in conjunction with a series of lectures dealing in more detail with the subject. To say, for instance, without qualification that penicillin 'is not of use' in colds, influenza and smallpox is to state a half-truth that can do more harm than good.

PSYCHIATRIST'S ANTHOLOGY

1005

Analecta Psychiatrica

J. R. Whitwell LONDON, H. K. LEWIS & CO. LTD., 1946. xvi + 160 PAGES. 22 x 14 cm. 16s. [£0.8]

(a) The psychological physician etc. (b) Tom o' Bedlam (c) forms of mental disorder etc. (d) suicide (e) causes, etc. of mental disorder (f) treatment (g) pathology etc. (eighteenth century) (h) some interesting cases etc. (i) tabular retrospect of psychiatry

The late Dr J R Whitwell was known to members of the Royal Medico-Psychological Association for many years. He was their Honorary Librarian and had spent years browsing quietly in the Library in Chandos Street where most of their treasures lay.

This small book is the result of years of reading, not amongst the ostentatious and distinguished looking modern books, but amongst the old books written by humble men who knew nothing of insulin, electric-shock or leucotomy (some of their treatments were much more drastic).

It consists of excerpts from most of the old writers from Hippocrates, Avicenna, Galen, Aristotle, through Shakespeare, Pope, Dryden, Burton to the reformers and kind-hearted men of the nineteenth century.

He quotes Andrew Boorde's (1490-1549 ?) *Breviary of Healthe* "Masters of the eximious and arcane science of physick, of your urbanity, exasperate not yourselves against me for making this little booke".

Those of us who are not yet "masters of the eximious and arcane science of physick" may nevertheless feel some "exasperation" that Dr Whitwell has rather ignored Andrew Boorde's contemporaries, the 15th-16th century herbalists.

Dodoens, as we read in Lyte's translation, provides us with a feast of prescriptions which are of the greatest interest to the reader in psychiatry "if the leaves or floures of Borage be put in wine, and that wine dronken, it wil cause men to be gladde and mery, and driveth away all heavy sadness and dull melancholie". "Thyme is profitable for those that are fearefull, melancholique, and troubled in sprite or minde", and again of the peony Dodoens says "Fiftene or sixtene of the black seedes dronke in wine or meade is a speciall good remedie for them that are troubled with the night Mare (which is a disease wherein men seeme to be oppressed in the night as with some great burthe and sometimes to be overcome with their enemies) and it is good against melancholique dreames". Aemeliu's *De virtutibus herbarum* tells us in verse the same quaint old remedies for "sickness of the minde".

This small omission apart, Dr Whitwell has given us a most interesting collection of writings from the old masters which are a sheer joy to read and re-read, and it is a pity he did not live to see its welcome.

G W T H Fleming

SURGERY

1006

617-089

Operative Surgery

G Bankoff LONDON MEDICAL PUBLICATIONS LTD, 1946
416 PAGES 479 ILLUSTRATIONS 22 x 14 cm. £3 3s. [£3 15]

(i) General operative technique, (ii) operations on blood vessels, (iii) operations on bones, (iv) orthopaedic operations on the extremities, (v) amputations, (vi) operations on lymph glands, (vii) operations on joints, (viii) operations on muscles and tendons, (ix) operations on peripheral nerves, (x) operations for infections of the hand, (xi) operations on the scalp, brain and skull, (xii) operations on the cranial air sinuses, (xiii) operations on the spinal cord, (xiv) operations on the face, (xv) operations on the jaws, (xvi) operations on the tongue and floor of the mouth, (xvii) operations on the neck, (xviii) operations on the thyroid gland, (xix) operations on the pharynx and oesophagus, (xx) operations on the air passages, (xxi) operations on the breast, (xxii) operations on the chest, (xxiii) the general principles of abdominal surgery, (xxiv) operations on the stomach and duodenum, (xxv) operations on the liver, gall bladder, and bile duct, (xxvi) operations on the pancreas, (xxvii) operations on the intestines, (xxviii) appendicectomy, (xxix) operations on the rectum, (xxx) operations for hernia, (xxxi) operations on the spleen, (xxxii) operations on the kidney and ureter, (xxxiii) operations on the bladder, (xxxiv) operations on the urethra, (xxxv) operations on the male genitals, (xxxvi) plastic repair, (xxxvii) repair of war injuries, (xxxviii) repair of injuries of the body, (xxxix) treatment of war fractures. Index.

The author of this book states that his prime object is to provide a concise treatise not for the specialist but for the student and general practitioner. This raises the question as to what should be provided for such a public. Since they do not specialize in surgery they would need only brief descriptions of major operations, but they would certainly require a full account of all those minor operations which they might be called upon to perform, only standardized and up-to-date techniques should be chosen, and brief notes might be inserted as to pre-operative and post-operative treatment. Judged by this standard, this book is inadequate.

The section on ligation of the blood-vessels is written on conventional lines and the chapter on amputations is commendably short, though several uncommon types of osteoplastic amputation of the lower limb are illustrated. For the most part, however, there is a lack of judgment in the choice of operations to be described. There is a very fully illustrated account of an operation for cleft-palate, but a much too brief description of the procedures which may be required in dealing with septic hand. The common operations for hallux valgus are sought in vain, instead we find described a complicated procedure which would need to be seen performed before it could be attempted. The technical descriptions of cholecystectomy, gastro-enterostomy, and excision of the rectum are too full of detail and rather difficult to follow. In the 14-line account of intestinal obstruction we are told that "immediate operation is imperative", without one word as to Wangensteen's method of intestinal decompression, similarly, in the section on acute osteomyelitis the advice is given that "as early an operation as possible is desirable" without mention of the value of penicillin in deferring the need for such operation. It is indeed startling to find in a book printed in 1946 that penicillin is not mentioned in the index, nor referred to even in the section on war injuries. In passing, we note that the author confuses laryngotomy with tracheotomy.

The book is well produced, printed on good paper and profusely illustrated, but one gets the impression that it is an ill-digested compilation rather than the outcome of extensive experience. It is not the type of book which we can recommend either for the student or general practitioner.

1007

617-001

The Principles and Practice of War Surgery

J Trueta THIRD EDITION LONDON HAMISH HAMILTON
MEDICAL BOOKS 1946 xvii + 426 PAGES 156 ILLUSTRATIONS
24 x 16 cm £2 2s [£2 1]

Preface to first edition, preface to third edition, Part I. The pathology of wounds and the treatment of the wounded patient (i) The biological principles of treatment, (ii) the development of war surgery, (iii) the healing of wounds, (iv) infection, (v) the passage of bacteria and their toxins through the body, (vi) pyogenic infections of war wounds, (vii) gas gangrene, (viii) tetanus, (ix) shock, (x) traumatic vascular spasm, (xi) blood transfusion, (xii) anaesthesia in wartime, Part II. The technique of wound surgery, a five-point programme (xiii) The essentials of treatment and organization (xiv) cleansing of the wound, (xv) chemotherapy, (xvi) wound excision, (xvii) drainage, (xviii) reduction and fixation of fractures, (xix) immobilization, (xx) plaster-of-Paris technique, (xxi) primary and secondary sutures, (xxii) skin graft in war surgery, (xxiii) articular wounds, (xxiv) amputation, (xxv) postural treatment, (xxvi) regional surgery, (xxvii) burns. Appendix I Bacteriology and progress of sulphanilamide treated wounds. Appendix II Experience since the invasion of Europe. Bibliography. Index.

The appearance of the third edition of this book on traumatic surgery proves that it has been both popular and useful to those members of the medical profession who have to deal with traumatic surgery, and it is indeed welcome to find such a practical volume on this subject written by a surgeon of considerable practical experience.

It is true that the publishers regret the end of the war occurring before this edition could be published. At least they spare us the recommendation that a new war should justify its appearance, and assuredly the increasing number of road accidents will make the volume welcome to the many surgeons who have to deal with these injuries.

The volume presents a well-arranged approach to the whole subject of traumatic surgery, and gives a clear disposition of its principles with which all surgeons of experience must agree.

In the preface Dr Trueta states that "perhaps the most important lesson of all is that there has been no effective substitute for correct surgery. Chemotherapy is an invaluable complement to timely cleansing, excision, drainage and immobilization, but when admitted as an alternative to these it can be a positive menace". The truth of this statement is all too obviously evident at the present time, and it is one that should be taken to heart by the whole medical profession, indeed, experience leads one to suggest that the early and adequate performance of correct surgical procedures requires emphasis.

Perhaps not sufficient credit is given to the work of the surgeons in the war of 1914/1918, for they, by painful experience, arrived at basic principles which were largely forgotten in the 20 years between the wars. Logie, for example, writing in 1943 on the Tobruk campaign, stresses that "The basic principles of surgery

are the same the whole world over", as though he had discovered some new fact, doubtless these principles are in danger of being forgotten in the future as they have been in the past, unless some grave mischance, such as arrogance bred in ignorance and fear, forces a war on us in the near future.

If we may be permitted to offer a few detailed comments while the publishers claim that a section on the transport of casualties is added, this is on such general lines and at such a high level that it is unlikely to be of much benefit to most surgeons, who are more concerned with the immediate problem of clearing casualties and judging which are in most urgent need of surgical intervention.

The sections on shock and gas gangrene are a valuable contribution to these subjects, though the indications for prophylactic treatment are perhaps not clearly set out.

The recommendation of pressure-plaster treatment as a routine for burns will be open to grave criticism by many British surgeons, whose war experience has led them to doubt both the safety and efficacy of this method of treatment, but as a disciple of the school of plaster treatment initiated by Croft and continued by Makins, Wallace and Max Page, the reviewer has nothing but praise for the closed plaster treatment of wounds and fractures, though one may disagree slightly with some details in the technique advocated.

Postural treatment in the after-care of these and other cases of trauma is rightly stressed as an important feature in preventing oedema and pain, and is one which is so often overlooked by many surgeons.

The book is a welcome addition to the library of any medical practitioner concerned with the treatment of injuries, but is perhaps inclined to stress the air-raid and traffic accident type of treatment as against the difficulties met with in those cases occurring in mobile and mechanical warfare. These difficulties are often, from our experience, not sufficiently emphasized, nor is sufficient credit given to the surgeons of the combatant medical services for the notable manner in which they were overcome, and surgery brought within reach of the front line casualty within that period of 6 hours which is so correctly advocated by Dr Trueta.

P H M

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NEW EDITIONS

61(92)

Notable Names in Medicine and Surgery

Hamilton Bailey & W J Baber SECOND EDITION LONDON
H. K. LEWIS & CO. LTD, 1946. viii + 202 PAGES 233 ILLUSTRATIONS. 19 x 13 cm. 12s. [£0.75]

The first edition of this volume of short biographies of familiar names in medicine and surgery has already been reviewed in these columns (*BMJ*, 1944, 2, 482/81). The second edition has not been altered extensively, but the illustrations have been improved and amplified.

1009

Antenatal and Postnatal Care

FRANCIS J BROWNE SIXTH EDITION LONDON J & A CHURCHILL LTD 1946. viii + 644 PAGES 90 ILLUSTRATIONS 21 x 14 cm. £1 5s. [£1.25]

(i) The history and development of antenatal care (ii) diagnosis of early pregnancy (iii) examination of the patient (iv) the hygiene of pregnancy (v) the influence of the emotions upon pregnancy and parturition (vi) constructive educational and social aspects of antenatal care (vii) the inheritance of morbid characters (viii) maturity and postmaturity (ix) abnormal presentations and positions (x) multiple pregnancy (xi) abnormalities in the quantity of amniotic fluid (xii) haemorrhage in early pregnancy (xiii) haemorrhage in early pregnancy (continued) (xiv) haemorrhage in early pregnancy (continued) (xv) unsuccessful pregnancy (xvi) the Rh factor and erythroblastosis (haemolytic disease of the new born) (xvii) haemorrhage in late pregnancy (xviii) haemorrhage in late pregnancy (continued) (xix) contracted pelvis and disproportion (xx) displacements of the uterus in pregnancy (xxi) vomiting in pregnancy (xxii) the toxæmias of late pregnancy (xxiii) diseases and disorders of the digestive system in pregnancy (xxiv) diseases of the circulatory system in pregnancy (xxv) diseases of the circulatory system (continued) (xxvi) diseases of the nervous system in pregnancy (xxvii) diseases of the nervous system (continued) (xxviii) diseases of the ductless glands in pregnancy (xxix) diseases of the ductless glands in pregnancy (continued) (xxx) diseases of the ductless glands in pregnancy (continued) (xxxi) diseases of the respiratory system in pregnancy (xxxii) diseases of the urinary tract in pregnancy (xxxiii) affections of the skin in pregnancy (xxxiv) tumours complicating pregnancy labour and the puerperium (xxxv) venereal diseases in pregnancy (xxxvi) the uses and value of radiology in obstetrics (xxxvii) postnatal care Appendix A. Antenatal record Appendix B. Discharge form Appendix C. Postnatal record Appendix D. Medicinal induction of labour Appendix E. Rhesus factor record Appendix F. Food list for low salt diets Appendix G. High protein diet. Index.

Professor F J Browne's well known textbook, which was first published in 1935, has reached its 6th edition, and is now the standard British work on the subject.

The text has been thoroughly revised throughout. Alteration has been found necessary chiefly in the chapters on erythroblastosis and the Rh factor, on placenta praevia, on the toxæmias of late pregnancy, and in that on venereal disease in pregnancy, to bring them into line with recent advances in knowledge. Short sections have been added on acroparaesthesia, angular pregnancy and on the influence of rubella and other infectious diseases in causing congenital abnormalities. The chapter on radiology in obstetrics has again been revised by Professor Chassar Moir.

1010

616-072 5

Sternal Puncture. A Method of Clinical and Cytological Investigation

A PIRRY & J L HAMILTON-PATERSON THIRD EDITION LONDON WILLIAM HEINEMANN (MEDICAL BOOKS) LTD 1946. xv + 80 PAGES 13 ILLUSTRATIONS 22 x 15 cm. 15s. [£0.75]

(i) The myelogram (ii) the marrow in leucæmia (iii) leucæmoid reactions (iv) neoplastic and allied conditions of the bone marrow (v) the anaemias (vi) erythraemia and allied states (vii) infective diseases (viii) hypoplasia and aplasia of the bone marrow (ix) some protozoal diseases (x) the technique of sternal puncture. Index.

The third edition of this monograph has been completely revised and enlarged in the light of the latest findings of bone marrow study. It provides for the student a convenient review of the information which is scattered throughout the literature. The illustrations have been revised, and now consist of 12 coloured and one black and white plates, provided as a visual guide to the use of sternal puncture in clinical pathology.

Guide to the Journals

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13 November 1946

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